# 55 Use of Food Supplements as Nutricosmetics in Health and Fitness
## *A Review*

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## INTRODUCTION

Nutrition has been defined as the biological process in animals and plants of food intake and its subsequent assimilation into the tissues. Nutritional (food) supplements are concentrated sources of nutrients (or other substances) with a nutritional or physiological effect that supplements the normal diet [1].

Nutricosmetics can be described as a recent result of a convergence phenomenon between cosmetics and food industries, still unfamiliar to many consumers and sometimes even to foods and cosmetics experts [2]. Nutricosmetics advertisements describe such oral supplementation of nutrients sometimes as "beauty pills," "beauty from within," "oral cosmetics," or "eat yourself beautiful." The nutricosmetics market was valued at $1.5 billion in 2007, but it was projected that it will reach $4 billion in 2015, with Europe as the most important market before Japan and the United States [3,4]. Nutricosmetics can be defined as ingestible products (pills or capsules, tablets, liquids, granulates, or foods) that are formulated and marketed specifically for beauty purposes [3]. Such products are at the intersection between nutrition and personal care, and they should not be confused with cosmeceuticals or nutraceuticals.

Cosmeceuticals are at the intersection between cosmetics (products that simply clean and beautify) and health care (products that cure and heal) [6] and are defined as topical cosmetic products that claim to have medical- or pharmaceutical-like benefits, while nutriceuticals are at the intersection between nutrition and health care and are foods or beverages providing health benefits including the prevention or treatment of disease (also called "functional foods") [2,3]. Figure 55.1 depicts that there is also a common intersection between the three types of care products, indicating that some nutricosmetic ingredients may not only act on skin, hair, and nails but also show more systemic (side) effects resulting in improved health and fitness. Nutricosmetics mostly claim an antiaging effect, for instance, by reducing wrinkles by fighting free radicals generated by solar radiation. Different conditions, such as ultraviolet (UV) radiation or exercise, contribute to reactive oxygen species (ROS) production in different human body tissues, which then can react with DNA, proteins, and fatty acids leading to oxidative damage and antioxidant system impairment. Therefore, antioxidants represent the most crucial among the nutricosmetical ingredients. The best-known antioxidants are carotenoids (beta-carotene, lycopene, lutein, zeaxanthin, and astaxanthin) and polyphenols (anthocyanidins, catechins, flavonoids, tannins, and procyanidins) [2,7]. Such antioxidants may also have important systemic effects on tissues other than skin. For example, they can scavenge singlet molecular oxygen ($^1O_2$) and peroxyl radicals or may influence signaling and gene expression at the muscle cell level during and after exercise.

The market for food supplements and nutricosmetics (French: "alicaments") is characterized by an important annual growth because today, consumers are aware of nutritional products that contribute to disease prevention, fitness, general health, and skin health. During the past decennium, industry developed many new nutritional applications to satisfy people's needs and demands such as protection of the skin from photo-oxidative (UV-induced) damage, which can occur, for example, after years of outdoor work or prolonged outdoor leisure and sports activities. This protection is recognized as beneficial to human health by the European Food Safety Authority (EFSA) Panel on Dietetic Products, Nutrition and Allergies [8].

While the nutricosmetic market is tiny in comparison to other personal care markets, it is estimated to be the fastest growing market (over 12% growth in 2007) [3]. This observed important growth in nutricosmetics is driven by different factors such as a shift toward less invasive treatments and beauty procedures, increasing consumer awareness (especially by the younger generation), rise of the spa and beauty culture, and environmental and societal factors. Furthermore, the increased life expectancy of the baby boomer generation in the industrialized countries demands new strategies to quality of life improvement including the need to appear youthful, fit, and healthy. In this context, nutricosmetics, besides cosmeceuticals and nutraceuticals, have emerged as a new strategy to prevent disease and to sustain general health and fitness while supporting skin health and beauty.

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This chapter tries to present an overview about (i) nutricosmetic ingredients that may not only act on skin, hair, and nails but also have a more systemic effect resulting in improved health and fitness; (ii) the possible working mechanisms of such health and fitness enhancing nutricosmetics, focusing on the carotenoid and phenolic ingredients; and (iii) the concept of combined nutricosmetical–cosmeceutical applications (i.e., combined oral and topical applications) and combined nutricosmetical–physiotherapeutical interventions (i.e., combined oral and exercise or massage applications).

## METHODS

The bibliography started with a systematic search in PubMed (search algorithm can be provided by the corresponding author on request). However, because of the high specificity of the topic "nutricosmetics as used in health and fitness" (Figure 55.1), the limited number of clinical trials in humans, and the exclusion of many papers reporting on care products such as mouthwash or toothpaste or on supplementation under extreme pathologic conditions such as HIV and AIDS or terminal cancer patients, the number of publications that could be retrieved meeting the criteria for this review question was very limited. Breaking down the combined search in more sensitive parts such as "antioxidant supplementation" yielded, on the other hand, a large amount of data available on such topics. Therefore, this review is not intended to be exhaustive but aims at giving an overview of the status quo on the evidence for the use of nutricosmetics in health and fitness.

## HISTORY OF COSMECEUTICALS, NUTRACEUTICALS, AND NUTRICOSMETICS

Historically, the cosmeceutical concept was created in 1961 by Reed, a founding member of the US Society of Cosmetic Chemists. The term "cosmeceutical" was, however, first used about 20 years later by Kligman [9]. Examples of such topical applied drug-like products are antiaging products, skin whiteners or brighteners, acne aids, whitening toothpastes, anticellulite products, or antiperspirants. The global cosmeceutical market is estimated to amount at $55 billion per year. DeFelice [10] first coined the term "nutraceuticals" in 1989. Nutraceuticals became a major focus of food and pharmaceutical companies in the 1990s. Examples of such oral drug-like products are cholesterol lowering, diabetes management, tartar control, digestive aid, and energizing and fitness-enhancing products. In 2012, the US manufacturer Wild Flavors Inc. launched and registered the trademark Vegiceuticals as a series of fruit and vegetable extract-based nutraceuticals [11]. Finally, nutricosmetics emerged as a segment of neutraceuticals, which first gained popularity in Japan and Europe. The development and market are dominated by beauty firms with only a few pharma or food entrants. The Swedish biochemist Dahlgren is one of the pioneers who invented the world's first nutricosmetic product in the late 1980s, called Imedeen [12].

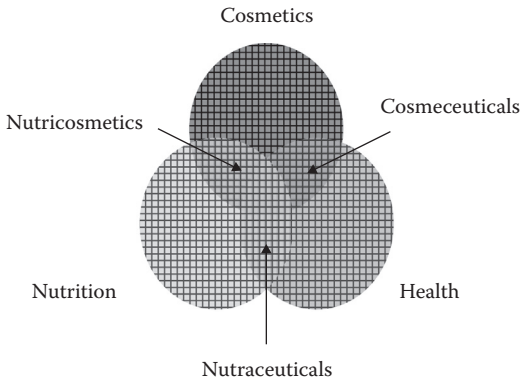


**FIGURE 55.1** Intersections between cosmetics, nutrition, and health. (Adapted from Carrie, M., Nutricosmetics: Decoding the convergence of beauty and healthcare, in *In-Costmetics*, Amsterdam, 2008.)

Differences in culture, legislation, and commercial climate between Europe, Japan, and the United States explain that the nutricosmetics market has developed independently in these geographic areas and thus has been tackled differently by the industry. Table 55.1 depicts different characteristics of the nutricosmetics markets in these three areas [5].

Industry believes that it will be very difficult for the US nutricosmetics market to reach the same level of penetration as Japan and Europe. Some top brands have already attempted to penetrate the market; however, they decided to exit again after minimal success. This may be partially explained by the observation that American consumers are less patient and generally less health conscious than their European and Japanese counterparts. Also, nutricosmetics lack good channel fit (e.g., pharmacies in the United States do not have the same influence as they do in Europe). Therefore, industry regards the US nutricosmetics market to be a nice add-on for professional skin care brands; however, it is predicted to remain a niche opportunity.

In the United States, especially consumers dislike the idea of buying ingestible products from cosmetic brands. Therefore, food and beverage manufacturers believed nutricosmetics to be a good opportunity and have tried to enter the nutricosmetic market over the last few years. Not all examples of food suppliers penetrating the nutricosmetic market were successful. For instance, Danone stopped the production of Essensis, which claimed to have skin hydrating properties above those of traditional moisturizing crèmes only 2 years after its appearance on the market. A French consumer organization disproved Danone's marketing claim through a clinical trial [13]. Another example illustrating that penetrating the nutricosmetics market can be difficult is Lumaé. In 2004, a US federal trademark registration was filed for Lumaé by Nestlé. Four years later, Coca Cola and L'Oréal launched the green tea-based health-and-beauty beverage called Lumaé, which claimed to address skin care needs. However, the current federal status of this trademark filing is "abandoned—no statement of use filed" [14]. In the context of

**TABLE 55.1**
**Characteristics of Nutricosmetics Markets in Europe, Japan, and United States**

| | Europe | Japan | United States |
|---|---|---|---|
| Application form | Tablets | Liquids | Tablets |
| Price | High | Low | Moderate |
| Distribution channel | Pharmacies | Mass mainstream | Specialty |
| Brands | Unique to Europe | Unique to Japan | Unique to United States |
| Benefits | Skin, hair | Beauty support, skin | Skin |
| Product claims | Specific | Vague | Vague to specific |

*Source:* Adapted from Carrie, M., Nutricosmetics: decoding the convergence of beauty and healthcare, in *In-Costmetics* 2008: Amsterdam.

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"nutriceuticals," however, Danone's probiotic yogurt Activia enriched with *Bifidobacterium lactis* DN-173-010 claims to support digestion of food, to produce certain vitamins, and to provide unfavorable conditions for some harmful bacteria, leading to improved digestive comfort and hence well-being, fitness, and health ("Feel the rhythm everyday with Activia"). According to the World Health Organization, probiotics are "live microorganisms which, when administered in adequate amounts, confer a health benefit on the host" [15]. Activia was backed by Danone Research with 17 published clinical studies, including seven on the strain survival and 10 on the benefit (6 related to transit and 4 to digestive comfort), and has been more successful than Essensis [16,17].

Hence, these examples may suggest that at least in European and US context, scientific investigation is a prerequisite to be successful when entering the nutricosmetics market, while Japanese consumers seem more willing to accept a rather holistic approach and to take such products mainstream without critically questioning their specific claims. In Europe, the legal framework exists under both food and medicinal law, but decisions as to which applies to nutricosmetics vary by country [5].

## PROPOSED WORKING MECHANISMS OF NUTRICOSMETICS AS USED IN HEALTH AND FITNESS

Nutrition can modulate the physiology and condition of different tissues and organic systems in the human body including the skin, cardiovascular system, the lungs, and the musculoskeletal system. Therefore, the understanding of the possible working mechanisms is partially derived from pathophysiological observations of organic or skin alterations under malnutrition conditions [1]. Nutricosmetics primarily aim at skin (antiaging, repair and prevention, sun protection, pigmentation, whitening, slimming), hair (retention and growth, restoration, nourishment, volumizing), and nails (strengthening). The ingredients should be safe and ingestible (often derived from food), and in general, they mostly offer an antioxidant, anti-inflammatory, or slimming function [3]. However, many products are being introduced in daily skin care antiaging cosmeceuticals or cosmetic products based on hypothetical in vitro mechanisms of action, without confirmation by controlled clinical trials [18]. The same may apply for nutricosmetics.

Nutricosmetics are usually based on combinations of the following ingredients: carotenoids, polyphenols, several vitamins, soy extracts (e.g., polyphenolic isoflavones), micronutrients, glycopolyglycans, amino acids, other plant-based elements (e.g., herbs), and polyunsaturated fatty acids (e.g., fish oils). The top nutricosmetic ingredients are collagen, co-Q10, grape-seed extract, green tea, lutein, lycopene, Marine Complex (deep sea fish ingredient), omega-3, superfruits (e.g., acai), vitamins A, C, and E, and zinc [4,12]. In the following section, the use of most of the aforementioned ingredients in (commercial) nutricosmetics and their suggested working mechanisms on skin (adnexes), health, and fitness together with scientific evidence will be discussed. However, while Chapter 54 discussed mainly the effects on skin, the following section has the intention of focusing on the (possible) nutricosmetic effects on health and fitness.

## CAROTENOIDS

In the following section, evidence based on simple solution studies, cell studies, and clinical trials will be discussed.

Aging seems to be associated with an increased oxidative stress resulting from an imbalance between free radical production and antioxidant defense [19]. Carotenoids (CARs) comprise a class of natural fat-soluble pigments (e.g., beta-carotene, lycopene, lutein, zeaxanthin, and astaxanthin), which are found in numerous fruits and vegetables. These $C_{40}$ carotenoids and their oxygenated derivates, the xanthophylls, are often used as antioxidant ingredients in nutricosmetics.

Furthermore, carotenoids may influence signaling pathways and gene expression at the cellular level of different tissues or enhance the intercellular gap junction communication [20].

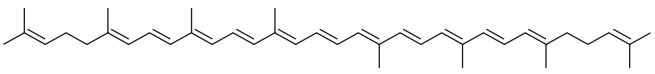

**FIGURE 55.2** Chemical structure of lycopene.

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As a nutricosmetic, there is convincing evidence that carotenoids are important components of the antioxidant network involved in the pathobiochemistry of several diseases affecting the skin and the eye. Within the retinal macula lutea, lutein and zeaxanthin are the predominant carotenoids acting as photoprotectors preventing its degeneration [21]. Their physicochemical properties make them suitable candidates for photoprotection of the retina against UV light-induced oxidative damage. While lutein and zeaxanthin accumulate mainly in the macula lutea, beta-carotene (provitamin A) accumulates preferentially in the skin providing it a "golden yellow" color. Beta-carotene is used as an oral sun protector preventing sunburns and has been shown to be effective either alone or in combination with other carotenoids or antioxidant vitamins.

The mechanisms observed in simple solvent and cell membrane model studies were supported by several cell-based studies. Based on the findings from clinical trials, there is evidence for carotenoid protection against sunlight-induced (long and short term) skin damage with treatment length as an important efficacy-influencing factor. Many other clinical trials on the effects of carotenoids (in general) and lycopene (in special) on different chronic diseases, such as the well-known prostate cancer studies, and on exercise capacity have been conducted.

Inneov Anti-Age Firming was launched as a nutricosmetic based on ingredients such as lacto-lycopene (similar to tomato lycopene), soy isoflavones, and vitamin C. The manufacturer recommends an intake of 2 capsules per day during 90 days. In 2010, researchers of the Inneov laboratory published a study that aimed to assess the effects of a nutricosmetic combining the probiotic *Lactobacillus johnsonii* (La1; has been reported to protect skin immune system homeostasis following UV exposure) and nutritional doses of carotenoids on early UV-induced skin damage. Three clinical trials (CT1, CT2, and CT3) were performed using different UV sources: nonextreme UV with a high UVA irradiance (UV-DL, CT1), extreme simulated solar radiation (UV-SSR, CT2), and natural sunlight (CT3). All three clinical trials were carried out in 139 healthy women over 18 years of age with skin type II–IV. In CT1, early markers of UV-induced skin damage were assessed using histology and immunohistochemistry. In CT2, the minimal erythemal dose (MED) was determined by clinical evaluation and by chromametry. Chromametry was also used to evaluate skin color. Dermatologists' and participants' assessments were compiled in CT3. The researchers found that a 10-week nutricosmetic intake prevented the UV-DL-induced decrease in Langerhans cell density and the increase in factor XIIIa+ type I dermal dendrocytes, while it reduced dermal inflammatory cells. Clinical and instrumental MED rose by 20% and 19%, respectively, and skin color was intensified, as shown by the increase in the DeltaE* parameter. The efficacy of the nutricosmetic was confirmed by dermatologists and participants under real conditions of use. Therefore, the researchers concluded that nutricosmetics combining the probiotic (La1) and nutritional doses of carotenoids reduced early UV-induced skin damage caused by simulated or natural sun exposure in a large panel of female participants ($n$ = 139). The authors further concluded that "this latter result might suggest that nutricosmetic intake could have a beneficial influence on the long-term effects of UV exposure and more specifically on skin photoaging" [22].

In athletes involved in sports with a high esthetic component such as dancers, rhythmic gymnasts, synchronized swimmers, body builders, and more recently, athletic pole dancers, a slightly tanned skin appearance may be wanted without UV radiation or the risk of smear of topical applied tanning sprays. The French nutricosmetic, Oenobiol Solaire, contains ingredients such as lycopene, luteine, selenium, and vitamin E, which support the melanin synthesis. Therefore, this nutricosmetic claims to have a natural photoprotective effect while supporting the tanning of the skin. The manufacturer recommends an intake of 1 capsule per day 1 month before, during, and 1 month after sun exposure. The manufacturer pretends that Oenobiol Solaire was backed with clinical trial validation. On the brand's Web site, an internal study is mentioned evaluating the effect of Oenobiol Solaire versus placebo in 50 participants followed up by dermatologists during 10 weeks showing 18.7% increase in tanning effect. Unfortunately, most of this research was internal and hence not published [23]. One such Oenobiol Laboratory study was found in Medline. The aim of this study was to demonstrate that modification of the cellular redox equilibrium occurs as a consequence of antioxidant nutrient intake (carotenoids, vitamin E, and vitamin C) and that these nutrients play a role in the pigmentation of the skin without any UV exposure. The researchers conducted a randomized, double-blind study in 20 healthy subjects to evaluate and compare the efficacy of two mixtures of dietary antioxidants with regard to direct determination of melanin and carotenes by chromametry at selected skin sites and multiple reflection spectrometry from a 1-$cm^2$ region of skin of different parts of the body. Efficacy was assessed by a significant improvement of these parameters, in comparison with measurements performed before nutricosmetic intake. The formulations per capsule of nutricosmetics under investigation were: 13 mg of beta-carotene, 2 mg of lycopene, 5 mg of vitamin E, and 30 mg of vitamin C (B13/L2) or 3 mg of beta-carotene, 3 mg of lycopene, 5 mg of vitamin E, and 30 mg of vitamin C (B3/L3). An 8-week B13/L2 supplementation led to a detectable carotenodermia, whereas the B3/L3 supplementation did not. An increase in melanin concentrations in skin was found after 4, 5, 6, and 8 weeks of dietary antioxidant intake in both groups ($p < 0.05$). The authors discussed these results with regard to the redox control theory of melanocytes, which regulate the tyrosinase activity [24].

Recent studies suggested that combined oral (nutricosmetic) and topical (cosmeceutical) treatments with the carotenoids lutein and zeaxanthin may increase skin elasticity, cutaneous hydration, and antioxidant protection and that the latter two effects were more pronounced in the combined oral and topical treatments compared to the isolated applications, hence suggesting a synergistic effect of nutricosmetic and cosmeceutical approaches [25].

While most knowledge about the carotenoid anti-oxidant working mechanisms comes from UV-induced skin damage

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studies, some information has also been derived from nutritional studies. Carotenoid-rich diets have been epidemiologically correlated with a lower risk for several diseases indicating that such antioxidants may also have important effects on several biologic tissues. Therefore, oral intake of nutricosmetics based on carotenoids may have "side effects" on other tissues than on the skin or eye leading to improved general health or physical (and mental) fitness status. For example, nutricosmetic carotenoids may help to interrupt the ROS damaging effects such as lipid peroxidation of the polyunsaturated fatty acids in biological membranes and blood (leading to impaired cell functioning) during and after strenuous exercise. Protective effects are also achieved with the tomato-derived lycopene (i.e., an exogenous carotenoid), also showing efficient singlet oxygen quencher characteristics. Following 10 to 12 weeks ingestion of lycopene or tomato-derived products rich in lycopene, a decrease in the sensitivity toward UV-induced erythema was observed in volunteers. Dietary carotenoids such as lycopene may contribute to lifelong photoprotective effects against harmful UV radiation [26,27]. Naturally derived lycopene seems to have a 25% higher effect compared to synthetic lycopene [28].

One study determined the relationship between concentrations of lycopene in human serum and other body tissues after tomato lycopene oleoresin supplementation (30 mg/day) or placebo administered for 1 to 7 weeks to 75 volunteers undergoing elective hemorrhoidectomy or perianal fistulotomy. Carotenoid concentration in blood and in the surgically removed skin and adipose tissues was measured by high-performance liquid chromatography (HPLC). The serum concentration of lycopene increased after supplementation from 0.26 ± 0.12 to 0.52 ± 0.25 μmol/l ($n = 35$; $p < 0.0001$), while in the placebo group ($n = 40$), lycopene serum concentration remained unchanged. Serum lycopene concentration after treatment was 2.2-fold greater in the lycopene group than in the placebo group, a slightly higher ratio than that found in skin and adipose tissue (1.6- and 1.4-fold higher than the placebo, respectively). These results show that tomato–oleoresin supplementation increases lycopene concentrations in serum, adipose tissue, and skin [29].

The observed ability to increase lycopene levels in tissues after supplementation is one of the prerequisites for using lycopene as an ingredient in a nutricosmetic with health and fitness benefits. Cardiovascular disease is associated with oxidative stress, inflammatory processes, and vascular dysfunction. As an antioxidant, lycopene has been suggested to protect against atherosclerosis based on its protective effect on lipid peroxidation; however, the exact mechanism of such protection is not yet clear [30].

One study on cell cultures investigated whether lycopene is able to counteract oxysterol-induced proinflammatory cytokine cascade in human macrophages, limiting the formation of atherosclerotic plaque. THP-1 macrophages were exposed to two different oxysterols, such as 7-keto-cholesterol (4–16 μM) and 25-hydroxycholesterol (2–4 μM), alone and in combination with lycopene (0.5–2 μM). Both oxysterols enhanced proinflammatory cytokine (interleukin [IL]-1beta, IL-6, IL-8, tumor necrosis factor alpha) secretion and mRNA levels in a dose-dependent manner, although at a different extent. These effects were associated with an increased ROS production through an enhanced expression of NAD(P)H oxidase. Moreover, a net increment of phosphorylation of extracellular regulated kinase 1/2, p-38, and Jun N-terminal kinase and of nuclear factor κB (NFκB) nuclear binding was observed. Lycopene prevented oxysterol-induced increase in proinflammatory cytokine secretion and expression, which was accompanied by an inhibition of oxysterol-induced ROS production, mitogen-activated protein kinase phosphorylation, and NF-κB activation (Figure 55.3). The inhibition of oxysterol-induced cytokine stimulation was also mimicked by the specific NF-κB inhibitor pyrrolidine dithiocarbamate. Moreover, the carotenoid increased peroxisome proliferator-activated receptor γ levels in THP-1 macrophages [31].

The protective effect of lycopene on atherosclerosis was supported by a random-effects model meta-analysis, summarizing the current evidence on the effect of lycopene supplementation of at least 2 weeks duration on serum lipid concentrations and blood pressure. Twelve studies (13 trial arms) investigated the effect of lycopene on serum lipids, and four studies examined its effect on blood pressure. A meta-analysis on serum lipids revealed a cholesterol-lowering effect of lycopene for total serum cholesterol (mean difference ± SE: −7.55 ± 6.15 mg/dl; $p = 0.02$) and low-density-lipoprotein (LDL) cholesterol (mean difference ± SE: −10.35 ± 5.64 mg/dl, $p = 0.0003$) in the subgroup of trials using lycopene dosages of ≥25 mg daily, whereas subgroup meta-analysis of trials using lower lycopene dosages was not significant. Meta-analysis of the effect of lycopene on systolic blood pressure of all trials suggested a significant blood pressure reducing effect (mean difference ± SE: −5.60 ± 5.26 mmHg, $p = 0.04$). This meta-analysis suggested that lycopene intake of ≥25 mg daily is effective in reducing LDL cholesterol by about 10%, which is a similar effect then of low statin doses in slightly hypercholesterolemia patients. More high-quality and large-scale studies are needed to confirm the suggested beneficial effects on total serum cholesterol and systolic blood pressure [32]. In commercial nutricosmetics (primarily aiming at the skin), lycopene concentration per capsule ranges from 2 [23] to 6 mg [33] per tablet or capsule. According to epidemiologic studies, tomato lycopene may also reduce the risk of prostate and several other cancer types. It was suggested that lycopene may have immunosuppressive properties, which

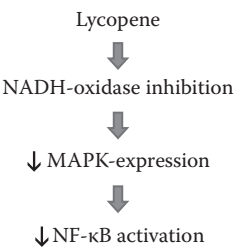


**FIGURE 55.3** Proposed pathway of the lycopene antioxidant and anti-inflammatory protective mechanism.

may be therapeutically useful in controlling chronic immune and inflammatory diseases [31]. Positive effects are also hypothesized in case of other diseases such as osteoporosis, neurodegenerative diseases, and hypertension, while adverse effects upon lycopene supplementation or lycopene toxicity have not been reported [34].

Based on its physicochemical properties, lycopene may also exert positive effects during and after exercise. In order to investigate the effects of lycopene on human ROS metabolism after high-intensity endurance exercises (a 4000-m run), a Chinese study randomly divided 70 college students into two groups: the intervention group (lycopene drink) and the placebo group (physiological saline drink). The students of each group were respectively given lycopene solution or physiological saline 45 min before running, and then each group took a lycopene solution or physiological saline drink at 1500-, 2500-, and 3500-m race distances, respectively. The blood samples were drawn before running and immediately after running to analyze proxies of ROS activity and oxidative tissue damage (such as malondialdehyde [MDA], a byproduct of lipid peroxidation), and total antioxidative capacity (TAC) levels were determined instantly. The results of this study indicated that the MDA level of the lycopene-supplemented group was significantly lower compared to the values observed in the control group ($p < 0.05$), while the TAC levels of the lycopene solution group were increased ($p < 0.05$). The authors concluded that lycopene supplementation can effectively enhance the person's antioxidation ability [35]. In another Chinese-controlled study, lycopene-supplemented athletes showed a delayed occurrence of exercise-induced fatigue and an improved immune function [36].

## POLYPHENOLS

Polyphenols represent a wide range of naturally occurring plant products, for example. anthocyanidins (berries), catechins (tea, apples, red wine), flavonols (green tea), flavavones (citrus fruits), isoflavones (soy), tannins (red grape), and proanthocyanidins (cacao, grape seeds), and contribute to the beneficial health and fitness effects of a diet rich in fruits and vegetables. Most evidence comes from in vitro as well as from in vivo observations from polyphenols such as flavonols, proanthocyanidins, silymarin, genistein, and resveratrol using both animal and human systems. Keratinocytes typically react to an acute and chronic UVB radiation with cyclooxygenase-2 (COX-2) expression and a subsequent prostaglandin (PG) metabolite secretion. COX-2 expression can be used as a proxy for inflammation and carcinogenesis.

UVB-induced COX-2 expression and PG metabolite synthesis can be inhibited by green tea (*Camellia sinensis*) polyphenol intake in mice experiments (Figure 55.4) [37].

The same pathway was proposed for the other phenols such as proanthocyanidins, silymarin, genistein, and resveratrol in mice studies, and therefore, the authors concluded that although more clinical studies are needed, supplementation of skin care products with green tea may have a profound impact on various skin disorders in the years to come [38].

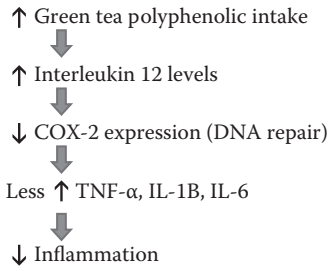


**FIGURE 55.4** Proposed pathway of the green tea phenolic anti-carcinogenetic protective mechanism.

This evidence is furthered with some clinical trials in humans. For example, tackling cellulite to increase a healthy and fit appearance is one of the most important aims of nutricosmetics. Inneov was launched as a green tea-based nutricosmetic aimed at decreasing cellulite. The manufacturer claims that based on internal studies in humans, "efficacy is proven by dermatological research and confirmed by female consumers" [39].

Also, in the context of health and fitness, the effects of polyphenolic antioxidants on exercise-induced oxidative stress have been studied in 30 male cyclists (23.6 ± 0.9 years) [40]. Based on the knowledge that intensive exercise may cause the perturbation of the physiological balance between oxidative reactions and antioxidant capacity in humans (i.e., oxidative stress; Figure 55.5), and that polyphenol-supplemented beverages are able to transfer their antioxidant capacity to body fluids [41], this controlled study (double-blinded randomized crossover design) investigated the effect of the flavonoid contents as the only antioxidant agent in a replacement drink designed for sportsmen on various oxidative stress biomarkers after two identical trials of submaximal aerobic exercise. The intervention trial participants consumed the antioxidant supplement (i.e., 2.3 g polyphenols/trial), while those in the control group consumed a placebo. Both at rest and after exercise (90 min at 70% $VO_{2max}$ bike ergometry) immediately and 45 min later, blood samples were collected to analyze plasma proxies of oxidative stress such as lipid oxidation (thiobarbituric acid reactive substances [TBARS]), total antioxidant status (TAS), protein oxidation, and the lactate dehydrogenase (LDH) and creatine kinase (CK) enzymes for each trial. All values were adjusted for changes in plasma volume.

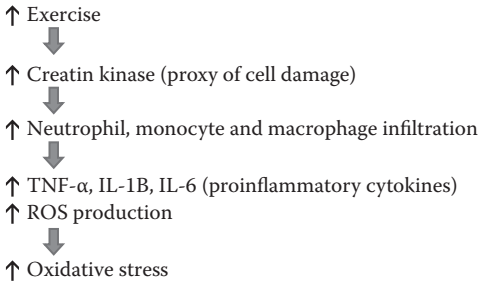


**FIGURE 55.5** Proposed pathway of the strenuous exercise–induced oxidative stress in muscle tissue. Flavonoids show capacity to interrupt this chain.

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The results showed no changes in plasma TAS and LDH after exercise or after the polyphenolic supplement. CK and TBARS increased after exercise in both tests. However, in response to strenuous exercise, the polyphenol-supplemented test showed a smaller increase in plasma TBARS and CK than the placebo test. CO increased by 12% in response to the placebo test, whereas it decreased by 23% in the polyphenol-supplement test. The authors concluded that this may indicate that the antioxidant supplement offered protection against exercise-induced oxidative stress [40].

## SOYBEAN ISOFLAVONES

Soy isoflavones are often used in nutricosmetics for their antioxidant and phytoestrogenic properties. For example, Imedeen Prime Renewal claims to "combat the effects of hormonal aging" and focuses on postmenopausal women. This nutricosmetic is based on ingredients such as MarineComplex (fish proteins and polysaccharides), soy extract, zinc, white tea, lycopene, grape-seed extract, chamomile, vitamin C, and vitamin E. The manufacturer recommends an intake of two tablets twice a day (in the morning and in the evening) and claims visible effects (e.g., reduced skin wrinkles) within 12 to 24 weeks. On the brand's Web site, links are uploaded to three reports of clinical studies on Imedeen Prime Renewal effects. Unfortunately, most of this research was presented only at congresses [12]. One study was found in evaluating whether MarineComplex affects skin morphogenesis differently in female and male human skin equivalents (HSEs). HSEs were established with cells obtained from female or male donors between 30 and 45 years of age and cultured for 7 or 11 weeks in the presence or absence of MarineComplex. Using immunohistochemistry, the researchers examined early differentiation by keratin 10 expression, (hyper)proliferation by keratin 17 and Ki67, and basement membrane composition by laminin 332 and collagen type VII. In addition, the expression of collagen type I and the secretion of pro-collagen I were measured. MarineComplex strongly increased the number of Ki67-positive epidermal cells in female HSEs. In the dermis, MarineComplex significantly stimulated the amount of secreted procollagen I and increased the deposition of laminin 332 and collagen type VII. Furthermore, MarineComplex prolonged the viable phase of HSEs by slowing down its natural degradation. After 11 weeks of culturing, the MarineComplex-treated HSEs showed higher numbers of viable epidermal cell layers and a thicker dermal extracellular matrix compared with controls. In contrast, these effects were less pronounced in male HSEs. The authors concluded that the MarineComplex nutrient positively stimulated overall HSE tissue formation and prolonged the longevity of both female and male HSEs. The ability of MarineComplex to stimulate the deposition of basement membrane and dermal components can be used to combat human skin aging in vivo [42].

Soy intake may have positive effects on bone and cardiovascular health. Based on a Bayesian meta-analysis including 17 randomized control trials (RCTs; humans), it was concluded that exposure to soy isoflavones can modestly, but significantly, improve endothelial function as measured by flow-mediated dilation. Therefore, exposure to isoflavone supplements may beneficially influence vascular health [43]. Another meta-analysis of 19 randomized placebo-controlled trials of at least 12 weeks duration concluded that soy intake (dietary, extract, or concentrate) as a phytoestrogen to prevent climacterium-attributed flashes in postmenopausal women showed a significant tendency in favor of soy, but that it is still difficult to establish conclusive results given the high heterogeneity found in the studies [44].

One meta-analysis was conducted to evaluate the effect of ingesting soy isoflavone extracts (not soy protein or foods containing isoflavones) on bone mineral density (BMD) in menopausal women. Eleven, seven, five, and five RCTs were selected for estimation of the effects on spine, femoral neck, hip total, and trochanter BMD, respectively. Meta-analyzing data from 1240 menopausal women showed that an average of 82 (47–150) mg soy isoflavones (aglycone equivalent) intake per day for 6 to 12 months significantly increased spine BMD by 22.25 mg/cm$^2$ (95% CI: 7.62 to 32.89 mg/cm$^2$; $p = 0.002$) or by 2.38% (95% CI: 0.93% to 3.83%; $p = 0.001$) compared with controls (random-effects model), while no significant effects on femoral neck, hip total, and trochanter BMD were found [45]. In the context of fitness, one study determined changes in body composition (BC), physical performance, metabolic and hormonal parameters induced by lifestyle counseling, resistance training, and resistance training with soy protein-based supplementation in 40 middle-aged males (50–65 years, BMI 25–29.9 kg/m$^2$). This RCT consisted of resistance training without or with a soy protein-based supplement and a control group with lifestyle education only. Changes in body weight (BW) and waist circumference (WC) were measured, and BC, fat mass (FM), and lean body mass (LBM) were measured by skin fold anthropometry at baseline and after 12 weeks of intervention. In addition, changes in physical fitness and metabolic and hormonal parameters (lipids, glucose, fructosamines, insulin, insulin-like growth factor-1, leptin, human growth hormone, dehydroepiandrosterone, testosterone, hs-CRP, Il-6) were evaluated. Thirty-five participants completed the 12-week study. No significant changes in BW were noted, although RM and WC dropped and LBM increased after training, particularly in the soy-supplemented group (FM: 22.6 ± 5.5 to 21.2 ± 4.7 kg; LBM: 68.5 ± 7.2 kg to 70.1 ± 7.4; $p < 0.01$). Subjects in the soy-supplemented group experienced more pronounced improvements in the strength measurements than the nonsupplemented resistance training group. After the training intervention, there were significant changes in hormonal and metabolic parameters as well as in glycemic control, particularly in the soy-supplemented group. The authors concluded that resistance training, particularly in combination with a soy protein-based supplement, improves BC and metabolic function in middle-aged untrained and moderately overweight males [46]. Soy isoflavones are also of interest to protect against exercise-induced ROS damaging of muscle cells [47].

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Another study was aimed to quantify the effects of Imedeen Prime Renewal on skin in postmenopausal women. It was a 6-month double-blind, placebo-controlled, randomized study on healthy postmenopausal females. Two tablets of Imedeen Prime Renewal or placebo were given twice daily for 6 months. Thirty-eight (active group) and 42 (placebo group) subjects completed the study out of 100. Clinical grading showed that the active group had a greater improvement ($p < 0.05$) compared to placebo for the face after 6 months treatment for forehead, periocular and perioral wrinkles, mottled pigmentation, laxity, sagging, under-eye dark circles, and overall appearance; skin on the décolletage after 2, 3, and 6 months of treatment; and skin on the hand after 3 and 6 months of treatment. Photo evaluation showed that the active group had a greater improvement ($p < 0.05$) on the face after 3 and 6 months for several parameters. Ultrasound measurements showed that the active group had a greater improvement ($p < 0.0001$) for density measurements after 6 months of treatment. Therefore, the researchers concluded that Imedeen Prime Renewal provides improved condition, structure, and firmness of the skin in postmenopausal women after 6 months [48].

## OTHER PLANT-BASED FLAVONOIDS

Examples of other bioflavonoids used in nutricosmetics are ginseng or ginkgo. Chronic supplementation of Panax ginseng (PG) (a deciduous perennial plant belonging to the Araliaceae family) enhances physical performance. In areas nearby the equator, athletes need to perform in a hot and humid environment due to the climatic characteristics of such regions. A Malaysian study evaluated the ergogenic effect of acute supplementation of PG on endurance performance in a hot and humid condition. Nine heat-adapted recreational runners (age: 25.4 ± 6.9 years, body mass: 57.6 ± 8.4 kg; body height: 168.3 ± 7.6 cm) were recruited in this placebo-controlled double-blind randomized study. Subjects ingested 200 mg of PG 1 h before the exercise test on treadmill at 70% $VO_{2max}$ in a laboratory environment of 31°C and 70% relative humidity. They drank 3 ml/kg BW of cool water every 20 min during the exercise to prevent adverse effects of dehydration. Blood samples were drawn every 20 min for the analysis of glucose, lactate, insulin, and free fatty acid levels. Oxygen uptake was determined every 20 min, while heart rate, body and skin temperatures, and ratings of perceived exertion (RPE) were recorded every 10 min during the trials. The researchers found that endurance running time to exhaustion did not differ between PG and placebo trials. Heart rate, skin temperature, core body temperature, oxygen uptake, RPE, plasma insulin, glucose, free fatty acid, and lactate levels during the endurance exercise did not show any significant differences between the trials. Therefore, the authors concluded that acute supplementation of 200 mg of PG did not affect the endurance running performance of the heat-adapted male recreational runners in the heat [49].

Over the last decennium, many in vitro and in vivo studies have suggested health and fitness enhancing effects of the phenolic compounds (mainly flavonoids such as catechin and epicatechin) of cocoa. For example, these bioactive molecules were found to have vasoactive properties and therefore may enhance endothelial function. In a double-blinded randomized crossover trial, 20 subjects received a 100 ml drink with high (176 to 185 mg) and low doses (<11 mg) of cocoa-rich flavan-3-ol (a flavonoid subclass). Upon ingestion, an increased flow-mediated dilution of conduit arteries was observed [50]. This finding was supported in a similar study with 11 smokers [51]. The mechanisms underlying the observed vasodilating effects are not yet well described, but there is evidence that the circulating NO pools are increased after flavonol cocoa consumption [51,52].

Among the other health-enhancing effects of cocoa are suppressed development of atherosclerotic lesions [53], decreased platelet function, increased skin microcirculation [54], inhibited proliferation of cancer cells in breast cancer patients [55], and hypoglycemic properties [56]. The main compounds are the procyanidin monomers (catechin and epicathechin), which showed antioxidant capacities [57–59]. In addition to these phenolic compounds, cocoa contains also methylxanthine (caffeine and theobromine), which was suggested to decrease the insulin-mediated glucose uptake and disposal as well as reduced lipid profiles in hypercholesterolemic animals [60]. A recent in vitro study supported the observation that the suggested antioxidant properties of cocoa are mainly based on the presence of the phenolic compounds. The methylxanthines, however, showed only low antioxidative capacities. Moreover, the presence of methylxanthines could even reduce the flavonoids' antioxidant properties [61].

Bark extract of *Pinus pinaster* has a long history of ethnomedicinal use and is available commercially as herbal dietary supplement with proprietary name Pycnogenol. It is used as a food supplement to overcome many degenerative disorders [62]. French maritime pine bark extract (*Pinus maritima*; Flavangenol) has gained popularity as a dietary supplement in the treatment of various diseases due to its polyphenol-rich ingredients. Oligometric proanthocyanidins (OPCs), a class of bioflavonoid complexes, are enriched in French maritime pine bark and have antioxidant and anti-inflammatory activity and a wide range of cardiovascular benefits such as lowered blood pressure, improved glycogemic control, lipid profile, fatty acid synthesis, and peripheral circulation [62,63]. A recent review described that the underlying mechanisms of these health- and fitness-enhancing maritime pine bark extract properties may be explained by studies showing evidence for their free radical scavenging activity, synergism with synthetic antioxidants, protecting biomolecules against oxidative damage, androgen synthesis stimulation, protective effect against I/R-induced oxidation, anti-inflammatory activities, and antimicrobial and antiviral activity [62].

One of the so-called "superfruit" ingredients of the nutricosmetics is based on extracts of the Amazonian palm berry, *Euterpe oleracea* (acai fruit). One animal cell-based study on mice peritoneal macrophages revealed the strong velutin (a flavone isolated from the pulp of the acai fruit) effects in

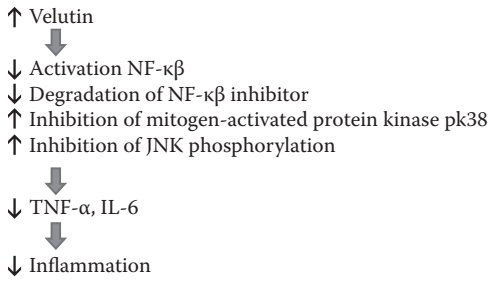


**FIGURE 55.6** Proposed pathway of the anti-inflammatory effects of velutin.

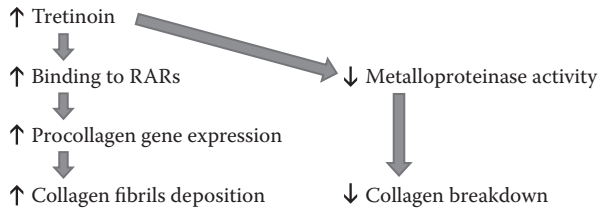


**FIGURE 55.7** Proposed pathway of the vitamin A effect on collagen fibers of the connective tissue of the skin (RAR = retinoic acid receptors).

reducing lipopolysaccharide-induced proinflammatory cytokines TNF-α and IL-6 production (Figure 55.6) [64].

Age-related diseases of the brain compromise memory, learning, and movement and are directly linked with increases in oxidative stress and inflammation. Because of their high polyphenolic content, fruit pulp fractions of acai were explored for their protective effect on BV-2 mouse microglial cells. Studies were conducted to investigate the mitigating effects of acai pulp extracts on lipopolysaccharide (LPS, 100 ng/ml) induced oxidative stress and inflammation. Treatment of BV-2 cells with acai fractions resulted in significant ($p < 0.05$) decreases in nitrite production, accompanied by a reduction in inducible nitric oxide synthase (iNOS) expression. The protection of microglial cells by acai pulp extracts can be explained by the pathway described in Figure 55.7. The current study offers valuable insights into the protective effects of acai pulp fractions on brain cells, which could have implications for improved cognitive and motor functions [65].

Taken together, the above-mentioned effects may play a significant role in the prevention of chronic inflammatory diseases, and hence, acai-based nutricosmetics may show promising effects for health and (mental) fitness. However, more human well-designed and large RCTs are needed to further verify these promising effects.

## VITAMINS

In commercial nutricosmetics, vitamins are nearly always present as a part of the formulation. Vitamin A is more frequently used in pharmaceutical products than in cosmeceuticals or nutricosmetics. Vitamin A, present in the human skin, cannot be synthesized; hence, it must be obtained through dietary means. The ingestion of vitamin A depends on the presence of retinoids (animal sources) and carotenoids (vegetable sources) in the diet. In the body, a small percentage of retinol is converted to its biologically active form, all-trans retinoic acid (tretinoin), through an intermediary, retinaldehyde. Most of retinol is converted to retinyl ester, its storage form. Topical retinoids have successfully been used to treat acne for nearly four decades [18]. Variations of this molecule have resulted in three generations of topical and systemic retinoids: the nonaromatics (retinol, tretinoin, and isotretinoin), the monoaromatics (etretinate and acitretin), and the polyaromatics (arotinoid, adapalene, and tazarotene). The efficacy of topical use of tretinoin in the treatment of photoaged and intrinsically aged skin is sufficiently evidence based. Figure 55.7 depicts the possible pathways resulting in an improved collagen deposition in connective tissue of the skin.

An overall thickening is observed in the epidermis: a compaction of the stratum corneum and deposition of a mucinous material (glycosaminoglycans) in the stratum corneum and intercellular spaces. The effects result in an improvement in the clinical and histologic skin appearance. However, the benefits of retinol and retinyl cosmeceutical products marketed as "antiaging" formulations are doubtful. They have varying low concentrations, and usually, there are a few clinical trials demonstrating efficacy. It seems that the useful concentration of topical retinol should range from 0.3% to 1%. Most of the over-the-counter products available usually contain lower levels of retinol (about 0.08% or less) [18].

Vitamin $B_3$ (nicotinamide or niacinamide) is a derivative of niacin obtained through diet from meat, fish, milk, egg, and nuts. Niacin has cholesterol-lowering properties. Nicotinamide is part of the coenzymes nicotinamide adenine dinucleotide (NAD) and NAD phosphate (NADP), and the reduced forms (NADH and NADPH) may act as antioxidants. NAD and NADP are important in many cellular metabolic enzyme reactions. Nicotinamide is involved in the synthesis of sphingolipids, free fatty acids, cholesterol, and ceramides (decreasing transepidermal water loss), in the suppression of melanosome transfer from melanocytes to keratinocytes, and it increases collagen production as was observed in a fibroblast culture study. All of these effects may help to reverse some of the aging (skin) signs, and for this purpose, it has been used in cosmeceutical products in concentrations ranging from 3.5% to 5%. There is certainly opportunity and interest to optimize use of this agent to achieve a higher performance [18].

The role of vitamin C as a free radical scavenger has been researched extensively. The water-soluble molecule functions in the aqueous compartment of the cell by donating electrons, neutralizing free radicals, and protecting intracellular structures from oxidative stress. L-ascorbic acid is essential for collagen biosynthesis. It serves as a cofactor for prolyl and lysyl hydroxylases, enzymes that hydroxylate proline and lysine in collagen, stabilizing its triple helical structure. Recent studies have demonstrated that vitamin C also influences collagen synthesis independently of hydroxylation by

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activating its transcription and stabilizing procollagen messenger ribonucleic acid [18]. Because of these antioxidant and collagen synthesis supporting mechanisms, vitamin C is often used in nutricosmetic formulations.

Throughout evolution, vitamin D (the sunshine vitamin) has been critically important for health. It has hormone properties and is produced in the skin or ingested from the diet and converted sequentially in the liver and kidneys to 1,25 dyhydroxyvitamin D. Vitamin D receptors are present in nearly every tissue cell in the human body. Therefore, vitamin D deficiency has been linked to increased risk for preeclampsia, requiring a cesarean section for birthing, multiple sclerosis, rheumatoid arthritis, types I and II diabetes, heart disease, dementia, deadly cancers, and infectious diseases. Therefore, sensible sun exposure along with vitamin D supplementation of at least 2000 IU/day for adults and 1000 IU/day for children is essential to maximize their health [66].

A Swiss review suggested strong evidence that higher 25-hydroxyvitamin D (25(OH)D) levels are protective against fractures and falls, while promising epidemiologic and mechanistic studies suggest a key role of vitamin D in the preservation of cardiovascular health and the prevention of cancer and other common chronic diseases. Lower extremity function, fall prevention, hip bone density, and fracture prevention optimal benefits are observed with 25(OH)D levels of at least 75 to 100 nmol/l. This threshold may be reached in 50% of adults with 800 to 1000 IU vitamin D per day [67].

It can be questioned, however, if the commercial nutricosmetics, available on the market today, reach the proposed health- and physical fitness-enhancing concentrations (1000 to 2000 IU vitamin D per day) in their formulations. Furthermore, the findings from observational and clinical studies on the association between vitamin D and physical performance remain controversial. A systematic review on the effects of low serum vitamin D concentration and vitamin D supplementation on muscle strength, balance, and gait performance among people aged 65 years and older was performed based on 16 studies (8 observational and 8 interventional studies) including 24 to 33,067 participants. Observational studies and clinical trials yielded divergent results, which highlights the complex and to date still poorly understood association between serum vitamin D concentration or vitamin D supplementation and physical performance [68].

Vitamin E is the major lipid-soluble antioxidant in the human body and, like vitamin A, is present in the skin. The probable physiologic function of epidermal vitamin E is to contribute to the antioxidant defense of the skin. Owing to its physical properties, vitamin E absorbs UV light in the solar spectrum. α-Tocopherol is the most active (from the eight existing vitamin E forms) and is important in protecting cellular membranes from lipid peroxidation by free radicals. Once oxidized, vitamin E can be regenerated back to its reduced form by vitamin C or L-ascorbic acid. Vitamin E has also an immunostimulatory effect, which has been shown to be associated with resistance to infections. Nutritional status is an important determinant of immune function. A double-blind, placebo-controlled trial determined the effect of 1-year supplementation with 200 IU/day vitamin E on the incidence and duration of respiratory infections in 617 elderly nursing home residents. The results of this clinical trial showed that vitamin E supplementation significantly reduces the incidence rate of common colds and the number of subjects who acquire a cold among elderly nursing home residents. Because of the high rate and more severe morbidity associated with common colds in this age group, these findings have important implications for the well-being of the elderly as well as for the economic burden associated with their care [69]. The effects may be partially explained by an increased enhancement of Th1, IL-2, and IFN-γ production [70,71]. However, the immunostimulatory effect of vitamin E may be reduced when ingested in combination with other supplements (such as fatty acids) as is usually the case in the context of nutricosmetics. For example, one study determined if concomitant consumption of fish oil and vitamin E would modify the vitamin E level needed for improving T cell-mediated function in elderly. This double-blinded RCT was conducted using 40 healthy male and female elderly subjects (>65 years) who were randomly assigned to one of four groups ($n$ = 10/group). All the subjects received 5 g of fish oil daily containing 1.5 g eicosapentaenoic acid (EPA) and 1 g docosahexaenoic acid (DHA), and a capsule containing different doses of dl-alpha-tocopherol (0, 100, 200, or 400 mg/day) for 3 months. Plasma vitamin E and fatty acid levels and in vivo (delayed-type hypersensitivity skin response [DTH] and T cell subpopulation analysis) and ex vivo (mitogen-stimulated peripheral blood mononuclear cell [PBMC] proliferation and IL-2 production) immune functions were determined at baseline and after supplementation. The authors concluded that the immuno-enhancing effect of vitamin E in the elderly is dampened when it is concomitantly consumed with fish oil. This may be due to the smaller increase in plasma concentrations of vitamin E in the presence of fish oil [72].

The available literature concerning the efficacy of systemic antioxidant substances such as vitamins, carotenoids, and vitamins, specifically C and E, is very extensive, but the results are often contradictory. For vitamin E, promising photoprotective effects were reported, specifically when it is combined with other antioxidants. However, more controlled studies especially on oral applied vitamin E in humans are needed before it can be recommended as an effective nutricosmetic agent for improved health and fitness.

## MICRONUTRIENTS

Zinc is one of the most used ingredients in nutricosmetics. Besides its described effects on the skin, a meta-analysis including four RCTS suggested potential benefits of zinc supplementation as a stand-alone intervention or as an adjunct to conventional antidepressant drug therapy for depression. However, there are methodological limitations in existing studies, and so further well-designed, adequately powered research is required [73].

Selenium is another commonly used nutricosmetic ingredient, mostly claimed to have photoprotective effects. In a

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large RCT, 974 men were randomized to either a daily supplement of 200 μg of selenium or a placebo. Patients were treated for a mean of 4.5 years and followed for a mean of 6.5 years. Selenium treatment was associated with a significant (63%) reduction of prostate cancer (relative risk, RR = 0.37, $p = 0.002$). There were significant health benefits also for total cancer mortality and the incidence of total, lung, and colorectal cancer; however, no protective effects against the squamous and basal cell carcinomas of the skin could be observed [74].

The effects of a choline-stabilized orthosilicic acid on the skin and hair in humans was investigated, and the results are described in Chapter 54.

Recently, the Panel on Dietetic Products, Nutrition and Allergies concluded that a cause-and-effect relationship has not been established between the consumption of a combination of lycopene, vitamin E, lutein, and selenium and protection of the skin from UV-induced (including photooxidative) damage [8].

## FATTY ACIDS

Omega-3 fatty acids [75] are micronutrients with known antiaging effects such as reduced wrinkle formation by protecting the skin against the damaging effects of UV light exposure. Oenobiol ("La beauté qui vient de l'intérieur") has been on the market since 1985 with its first product called "Fortepa 500," an essential fatty acids-based hydrating capsule for female consumers.

## COLLAGEN, GLUCOSAMINE, AND CHONDROITIN

One study assessed the incidence of total joint replacement (TJR) during the long-term follow-up of patients with knee osteoarthritis (OA) formerly receiving treatment with glucosamine sulfate or placebo. Knee OA patients participating in two previous randomized, placebo-controlled, double-blind, 3-year trials of glucosamine sulfate and receiving treatment for at least 12 months were systematically contacted to participate in a long-term follow-up retrospective assessment of the incidence of total knee replacement. Out of 340 patients with at least 12 months of treatment, 275 (81%) could be retrieved and interviewed for the present evaluation: 131 formerly on placebo and 144 on glucosamine sulfate. There were no differences in baseline disease characteristics between groups or with the patients lost to follow-up. The mean duration of follow-up was approximately 5 years after trial termination and treatment discontinuation, making up a total of 2178 patient-years of observation (including treatment and follow-up). Total knee replacement had occurred in over twice as many patients from the placebo group, 19/131 (14.5%), than in those formerly receiving glucosamine sulfate, 9/144 (6.3%) ($p = 0.024$, chi-square test), with a relative risk that was 0.43 (95% CI: 0.20 to 0.92), that is, a 57% decrease compared with placebo. The Kaplan–Meier log-rank test survival analysis confirmed a significantly decreased ($p = 0.026$) cumulative incidence of total knee replacements in patients who had received glucosamine sulfate. A pharmacoeconomic analysis in a subgroup of subjects suggested that patients formerly on glucosamine sulfate had recurred to less symptomatic medications and use of other health resources than those from the placebo group during the last year of follow-up. The authors concluded that treatment of knee OA with glucosamine sulfate for at least 12 months and up to 3 years may prevent TJR in an average follow-up of 5 years after drug discontinuation [76]. An extensive indirect comparison meta-analysis determined the effect of glucosamine, or chondroitin, or both combined joint pain and on radiological progression of disease in OA of the hip or knee. Direct comparisons within trials were combined with indirect evidence from other trials by using a Bayesian model that allowed the synthesis of multiple time points. Ten trials in 3803 patients were included. On a 10-cm visual analogue scale (VAS), the overall difference in pain intensity compared with placebo was −0.4 cm (95% CI: −0.7 to −0.1 cm) for glucosamine, −0.3 cm (95% CI: −0.7 to 0.0 cm) for chondroitin, and −0.5 cm (95% CI: −0.9 to 0.0 cm) for the combination. For none of the estimates did the 95% credible intervals cross the boundary of the minimal clinically important difference. Industry-independent trials showed smaller effects than commercially funded trials ($p = 0.02$ for interaction). The differences in changes in minimal width of joint space were all minute, with 95% credible intervals overlapping zero. Therefore, the authors concluded that compared with placebo, glucosamine, chondroitin, and their combination do not reduce joint pain or have an impact on narrowing of joint space. Health authorities and health insurers should not cover the costs of these preparations, and new prescriptions to patients who have not received treatment should be discouraged [77].

Glucosamine appears to be the rate-limiting substrate for hyaluronic acid production in the wound. Adequate dietary protein is absolutely essential for proper wound healing, and tissue levels of the amino acids arginine and glutamine may influence wound repair and immune function. The botanical medicines *Centella asiatica* and aloe vera have been used for decades, both topically and internally, to enhance wound repair, and scientific studies are now beginning to validate efficacy and explore mechanisms of action for these botanicals. To promote wound healing in the shortest time possible, with minimal pain, discomfort, and scarring to the patient, it is important to explore nutritional and botanical influences on wound outcome [78].

BioCell Technology launched its BioCell Collagen as a nutricosmetic that promotes both active joints and younger looking skin. It is a chicken sternal cartilage derived, low molecular weight extract consisting of a matrix of hydrolyzed collagen type II and low-molecular-weight hyaluronic acid and chondroitin sulfate [79]. One pilot open-label study investigated the effect of BioCell Collagen in 26 healthy females who displayed visible signs of natural and photoaging in the face. Daily supplementation with 1 g BioCell Collagen for 12 weeks led not only to significantly increased skin properties but also to a significantly increased hemoglobin content (15%, $p = 0.008$) [80].

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OA is an important source of pain and disability. One randomized, double-blind, placebo-controlled trial has investigated the efficacy of BioCell Collagen, in the treatment of OA symptoms. Patients ($n = 80$) had physician-verified evidence of progressive OA in their hip and/or knee joint. Joint pain had been present for 3 months or longer at enrolment. Subjects were divided into two groups and administered either 2 g of BioCell Collagen or placebo for 70 days. Outcome measurements included VAS for pain and Western Ontario and McMaster Universities Arthritis Index (WOMAC) scores taken on days 1, 35, and 70. Intention-to-treat analysis showed that the treatment group, as compared to placebo, had a significant reduction of VAS pain on day 70 ($p < 0.001$) and of WOMAC scores on both days 35 ($p = 0.017$) and 70 ($p < 0.001$). The BioCell Collagen-supplemented group experienced a significant improvement in physical activities compared to the placebo group on days 35 ($p = 0.007$) and 70 ($p < 0.001$). The authors concluded that BioCell Collagen can be considered a potential complement to current OA therapies [81].

## CONCLUSIONS

In the literature, the results from clinical trials on the benefits (or harms) of nutricosmetics on skin, health, and fitness are still confusing. This can be partially explained by the diversity of the used research methods. For instance, in clinical trials on the effects of carotenoids, many different carotenoid concentrations are studied, with many different end points, trial durations, and seasonal differences, different types of subjects and patients, and different measurement instruments. Some studies were not controlled (i.e. single arm prepost study design), while in other studies, it was not clearly described if it was a randomized clinical trial and/or if allocation was concealed or if participants, researchers, or observers (e.g., statisticians) were blinded. Most studies were characterized by small sample sizes and hence may be underpowered. Furthermore, in the carotenoid trials, the role of oxidative metabolites and the isomerization status of the carotenoids may increase the heterogeneity of the study results. Another real threat is the so-called "internal research" of manufacturer laboratories, not willing to publish the trial results in peer-reviewed journals. Together with the fact that small nonsignificant trials tend to be less published, this may lead to publication bias. Therefore, large and high-quality (randomized) clinical trials with low risk of bias are needed to further the evidence for the use of nutricosmetics in health and fitness. Industry itself realized that clearly documented and independent scientific research findings should be published [5]. This is also of crucial importance to be successful as a manufacturer of nutricosmetics, especially in the European market with well-informed critical consumers.

It is important to understand the science behind nutricosmetics as they are increasingly becoming popular as skin care products in Europe and Japan. Many compounds of commercial nutricosmetics also show promising health- and fitness-enhancing properties. Phenolic compounds and vitamins, for example, are strong antioxidants. However, depending on their concentrations, promising antioxidants may behave as prooxidants. Also, the low antioxidant methylxanthines may reduce the antioxidant effects of flavonoids in mixed formulations or even start to behave as prooxidants. This may induce unintended side effects. It can be argued that the concentrations of some of the bioactive compounds (such as the vitamins) in commercial nutricosmetics may be too low to have an effect on health and fitness. Marketing offices of manufacturers are ahead of their scientific departments. Nutricosmetic specific studies are lacking. Most studies are in vitro or in vivo animal studies on oral supplements. High-quality, large randomized controlled trials in humans and meta-analyses including such high-quality RCTs are needed before nutricosmetics can be recommended to be used for health and fitness.

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