A Market Overview of Nutricosmetics

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The aging population spends billions of dollars each year on vitamins, minerals, botanical extracts, and antioxidants in an effort to maintain a youthful appearance of the skin and promote overall well-being. Hormonal imbalance, inflammation, smoking, exposure to UV radiation, and environmental stressors contribute to the aging of the skin by production of reactive oxygen species (ROS) that can potentially damage cell membranes, proteins, and DNA. This overload of oxidative stress and a production of free radicals can eventually break down connective tissues and collagen, and release chemicals that lead to cellular and molecular events that are evident as signs of aging, such as the formation of wrinkles, uneven skin tone, dyspigmentation, inflammation, immunosuppression, photoaging, photocarcinogenesis, and sagging skin. Nutricosmetics provide nutritional antioxidant supplementation to support endogenous antioxidant enzymes that may help to internally regulate oxidative stress and help to achieve a healthier skin appearance from the inside out. This article reviews the various theories behind the process of skin aging, the role of antioxidant enzymes in the prevention of skin aging, and the endogenous and exogenous antioxidants that may help to minimize the effects of oxidative stress.

The nutricosmetics market was worth $1.5 billion in 2008, according to Euromonitor International, with 95% of sales generated in Europe and Japan. Due to stringent regulations, the US market lags behind, but interest is growing as Americans become acquainted with a wide array of functional foods and drinks that promote health.[1] The concept of nutricosmetics is based on the theory that the key to a beautiful face is a healthy body. The idea of capitalizing on active nutritional ingredients to promote skin health first arose in the 1980s. Ever since then the industry has been witnessing a constant inflow of innovative formulations, the latest being oral antiaging supplements.[2]

Oral cosmetics, beauty foods, and antiaging cocktails define a group of products that determine "beauty from within." They contain vitamins, minerals, botanical extracts, and antioxidants in their composition that have an effect on the body and face, and are purported to optimize skin health.

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Dr. Madhere has provided physician testimonial for GliSODin Skin Nutrients, manufactured by Isocell. Ms. Simpson reports no conflict of interest in relation to this article.

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INTRODUCTION

The class of products known as *nutricosmetics* represents the intersection between personal care and nutrition. Several key factors drive the nutricosmetic market, including: the aging population, which currently spends billions of dollars each year in an effort to maintain a youthful appearance and promote overall well-being; the increasing awareness of the link between diet and health,

including physical appearance, and consumers are more open to the concept of "beauty from within"; and the continuing research and development of active nutritional ingredients for skin health.[3]

Nutricosmetics contain active nutritional ingredients that can bypass several barriers, including bioavailability and biodistribution, to be delivered effectively to the skin (the target organ). These active nutritional ingredients enter from the inside and move toward the outer layer. They are found in the deeper layers of the skin where they can work effectively through protecting the skin from oxidative stress and promoting healthy skin-cell turnover.[4]

Combining both topical and orally administered skin care products as part of a daily beauty regimen is gaining popularity, and scientific studies show that there are synergies to be gained from a combined topical and oral beauty program.[4-21]

SKIN AGING AND OXIDATIVE STRESS

Skin aging is a complex and natural phenomenon characterized by progressive deterioration of physical and functional properties. Skin aging is considered a degenerative process affected by both intrinsic and extrinsic factors. Intrinsic factors occur physiologically and are related to the changes that take place on a cellular level, such as a reduction in dermoepidermal papillae in the stratum corneum, a decrease in the thickness of the dermis, an increase in skin laxity, and a reduction in both dermal collagen production and connective tissue components.[22] A number of extrinsic factors also are thought to contribute to skin aging, including photodamage, smoking, and other exogenous stimuli. There are a number of theories[12,23] that seek to determine the primary causes of aging overall. Some of these proposals also surmise that the same factors that may influence aging also may contribute to the aging effects on the skin.

One theory that may in part explain the process of skin aging is that of oxidative stress. Oxidative stress occurs when cells produce reactive oxygen species (ROS), also known as free radicals, in excess of the ability of the body to reduce the number or counter the effects of potentially detrimental metabolites of oxygen. The oxidative stress theory of aging, therefore, purports that increases in ROS production underlie the aging process, which leads to functional abnormalities, pathological conditions, and other alterations from normal homeostatic mechanisms.[24] Reactive oxygen species are more reactive than molecular oxygen, are thought to be involved in a plethora of physiologic alterations and include the superoxide (O_2-) and hydrogen peroxide (H_2O_2) radicals. Reactive oxygen species are generated primarily intracellularly through mitochondrial processes. However, exogenous stimuli, such as infection, radiation, various drugs, and environmental stress have been known to lead to the production of ROS. The accumulation of these damaging oxygen species, therefore, may play a plausible role in skin aging de novo or by exacerbating the decline in skin function that manifests as skin aging.[23,25-27]

The factors that can accelerate skin aging are numerous and may include hormone imbalance, inflammation, smoking, and exposure to UV radiation. Moreover, as the skin ages, the cells are more susceptible to environmental stressors. These stressors stimulate the production of free radicals that can potentially damage cell membranes, proteins, and DNA. This oxidative overload of free radicals can eventually break down connective tissues and collagen, and release chemicals that lead to cellular and molecular events that are evident as the formation of wrinkles, uneven skin tone, dyspigmentation, and sagging skin.[4,7,23,25-27]

While there is compelling scientific literature to support the role of oxidative stress in aging, a direct cause-and-effect relationship has not been solidly established. Nevertheless, the demand for knowledge on the mechanisms of aging and how to manage these changes remains strong. Thus, a number of studies[4,6-21,23,25-36] have observed the positive effects of antioxidants in reversing or potentially preventing some of the adverse sequelae of ROS-induced free radical damage It can be argued that molecules or substances that reduce the oxidative load may be able to intervene along the cascade that leads to the degenerative changes of aging and aging skin by restoring a stable balance between ROS and the natural repair and defense mechanisms of the body. In light of this, in the skin antiaging and beauty industries, nutricosmetics or nutraceuticals have been put forth as antioxidants that will help to internally regulate oxidative stress and help to achieve a healthier skin appearance from the inside out. It has been stated that nutricosmetics generally address the following specific areas for skin: 1) photoprotection, 2) pigmentation, and 3) hydration. Although the exact mechanism of action of some nutraceuticals is difficult to specify due to a heterogeneity of studies, it is clear that antioxidants function to neutralize the detrimental effects of ROS. This may serve as a plausible position from which to further investigate and establish whether there is a direct relationship between oral antioxidant supplementation and aging. Moreover, there are independent case studies that suggest that a reduction in inflammation resulting from ingestion of antioxidants may have had a positive effect on patients with acne vulgaris.[7,8,23,27-30] While there is a need for controlled trials to evaluate the role of antioxidants in aging and disease, there is anecdotal evidence to suggest that if antioxidants

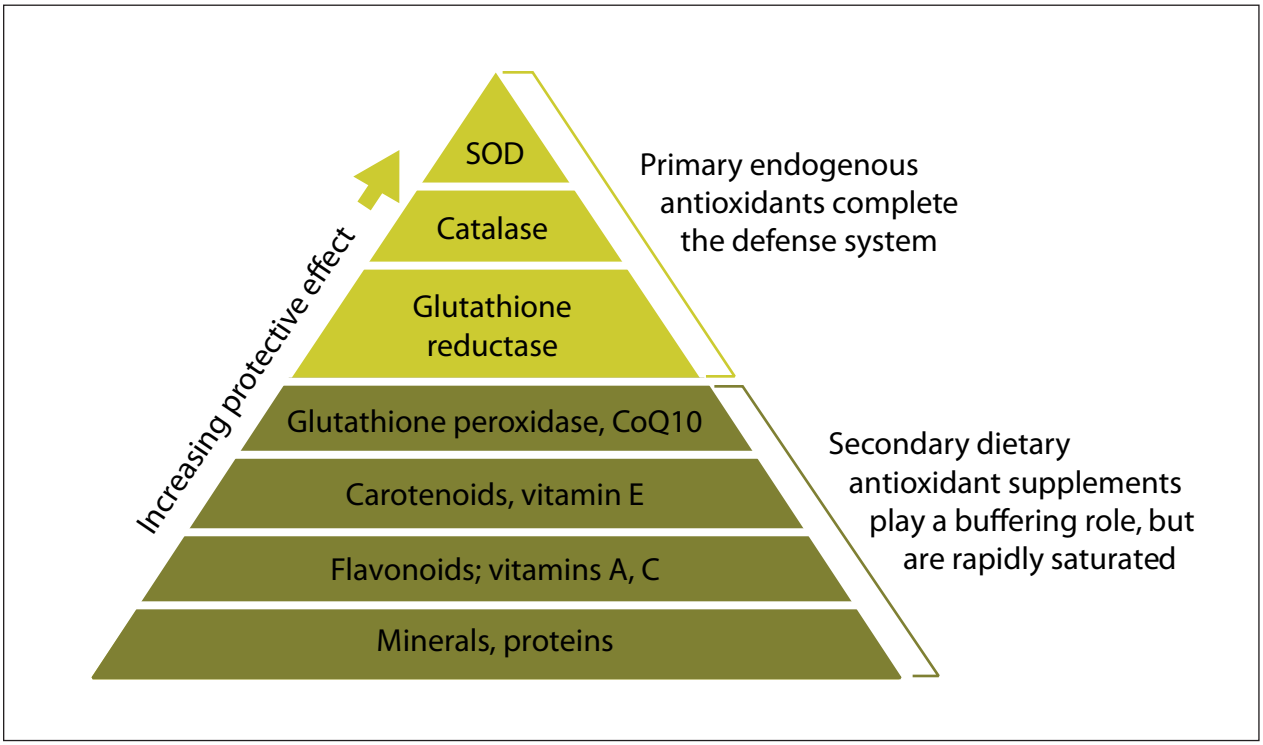

Figure 1. Endogenous and exogenous antioxidants that combat oxidative stress. SOD indicates superoxide dismutase; CoQ10, coenzyme Q10.

do not directly ameliorate free radical damage, then they may at least complement well-established therapies safely and effectively.

ENDOGENOUS ANTIOXIDANTS

The natural (intrinsic) aging of the skin is enhanced by environmental factors (extrinsic aging). One of the most important environmental factors is the solar UV exposure, which results in photoaging.[6] UV-mediated cellular damage occurs primarily through the release of ROS and is responsible for inflammation, immunosuppression, photoaging, and photocarcinogenesis.[7] Arachidonic acid (AA) metabolites and histamine that are found in increased amounts in skin inflammation are thought to play a key role in the induction of postinflammatory hyperpigmentation. Increased proinflammatory mediators in sunburned skin, particularly AA metabolites and tyrosinase activity, also are thought to stimulate melanocytes in the production of hyperpigmentation.[8]

Natural defenses against oxidative stress include endogenous antioxidant enzymes, particularly superoxide dismutase (SOD), catalase, glutathione reductase, glutathione peroxidase.[28,29] These enzymes also are present in skin and are involved in the protection against oxidative stress. UV radiation-induced cutaneous injury may occur under conditions of high oxidative stress when endogenous antioxidant defense mechanisms are overloaded. At this point, secondary exogenous dietary antioxidant supplements are anticipated to reduce the negative effects of UV radiation exposure (Figure 1).[27-30]

EXOGENOUS ANTIOXIDANTS

Superoxide Dismutase

A unique combination of SOD extracted from cantaloupe (*Cucumis melo* Linnaeus) with a wheat gliadin biopolymer (GliSODin) has been shown to offer therapeutic means for the prevention and treatment of many conditions associated with increased oxidative stress and inflammation (including skin-protecting benefits) in over 20 clinical studies.[27]

Oral administration of SOD and the other antioxidant enzymes present in many plant extracts is not effective under normal conditions. During passage through the gastrointestinal pathway the enzyme is denatured (deactivated) rendering it ineffective as an antioxidant. However, studies have shown that combining SOD with a wheat gliadin biopolymer system temporarily protects the SOD during its passage through the gastrointestinal tract.[30] The antioxidant enzyme SOD has a distinct

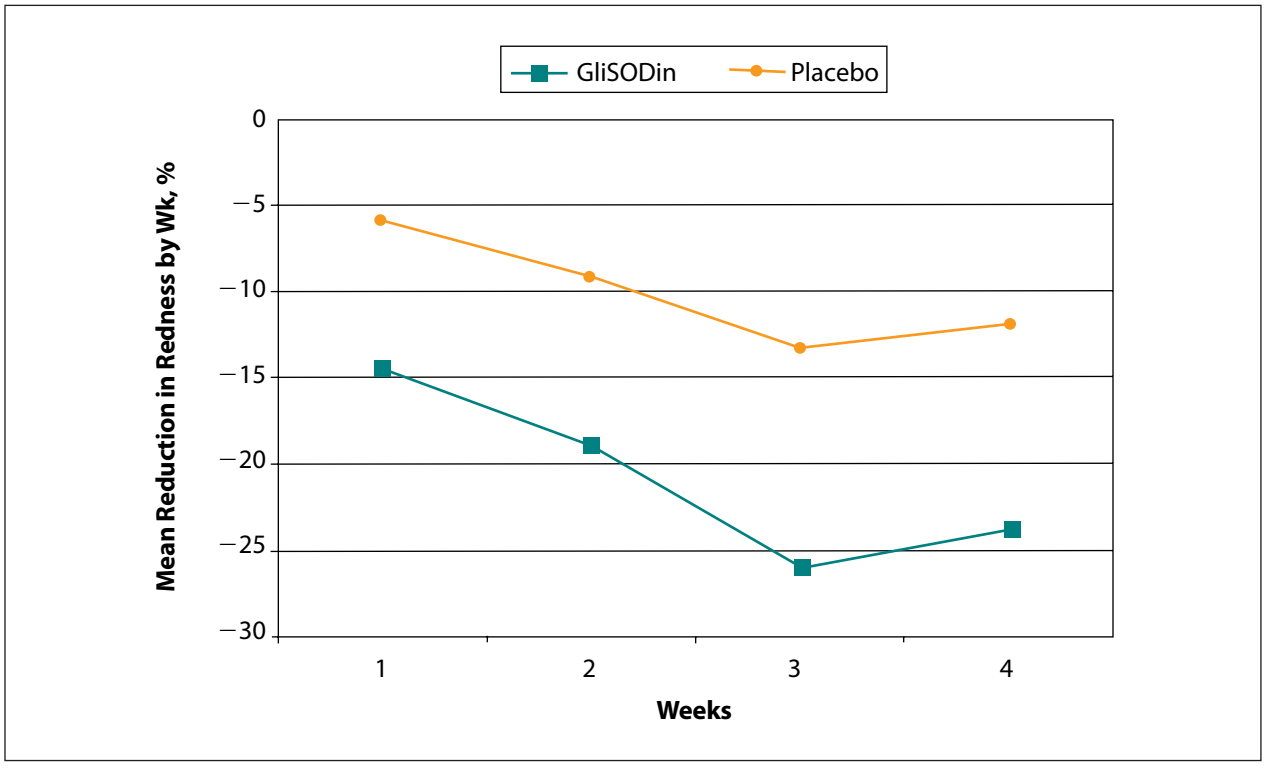

Figure 2. Mean percent reduction in redness over 4 weeks in the GliSODin and placebo groups.

advantage over the antioxidants consumed from the diet alone or nutritional supplements, like the vitamins A, C, and E, because this enzyme works as a biological catalyst that rapidly and repeatedly reduces ROS without being consumed. Like most other protective mechanisms in the body, the production of SOD decreases with age, while exposure to endogenous and exogenous stressors increases with age.[31]

In a randomized double-blind clinical trial, GliSODin supplementation reduced skin-reddening when healthy fair-skinned participants were exposed to UV radiation.[9,32,33] Fifty participants were randomly assigned to receive a daily dose of GliSODin (500 mg) or placebo for 4 weeks. Participants in the GliSODin group demonstrated an increase in the minimum exposure to UV radiation necessary to produce sunburn for fair-skinned participants (Fitzpatrick skin type II), compared to participants in the placebo group. The induced redness also decreased quicker in the GliSODin-supplemented group over the 4-week period. These results confirmed the efficacy of the SOD-gliadin combination against the consequences of oxidative stress produced by exposure to UV radiation. However, in a later study of similar design that included participants with Fitzpatrick skin type II, GliSODin notably increased the minimal erythema dose within 2 weeks with a dose of just 250 mg (Figure 2).[9,32,33]

Carotenoids, Minerals, Cocoa Flavonoids, and Marine Fish Oils

Lycopene belongs to a group of physiological compounds known as carotenoids. Tomatoes (particularly tomato paste) contain high concentrations of lycopene, phytoene, and phytofluene, and smaller quantities of beta and zeta carotene. A growing body of research is showing protective benefits of lycopene from the detrimental effects of oxidative stress (including photoprotection for the skin).[10-12]

Césarini et al[13] investigated the capacity of an antioxidant complex (AOC) containing vitamins (lycopene, beta carotene, alpha tocopherol, and selenium) to reduce UV-induced damage in 25 healthy participants. The AOC was orally administered daily during 7 weeks. After the oral intake of an AOC, many parameters of the epidermal defense against UV-induced damages were substantially improved. Researchers concluded that oral AOC supplementation could provide a safe, daylong and efficient complement to photoprotective measures provided by topical and physical agents and may contribute to a reduction in damage to DNA that leads to skin aging and skin cancers.[13]

In another study, researchers investigated the effect of a tomato-based drink on markers of inflammation, immunomodulation, and oxidative stress. In a placebo-controlled,

double-blind, crossover study participants were given either Lyc-o-Mato (5.7 mg of lycopene, 3.7 mg of phytoene, 2.7 mg of phytofluene, 1 mg of beta carotene, and 1.8 mg of alpha tocopherol) or placebo for 26 days, separated by a wash-out period. At the end of the trial, results showed tumor necrosis factor α production by whole blood was 34.4% lower after 26 days of the tomato-based drink consumption.[14]

Studies have shown the selenium-dependent glutathione peroxidase enzyme activity is low in participants with acne vulgaris. One study examined the effect of selenium and vitamin E (0.2 mg of selenium plus 10 mg tocopherol succinate twice daily for 6 to 12 weeks) in participants with acne vulgaris. The combination of selenium and vitamin E led to improvements in acne vulgaris, especially in participants with low baseline glutathione peroxidase activity.[15,16]

In addition to selenium, copper, molybdenum, and zinc are involved in many biochemical processes that protect the skin from oxidative stress. These minerals are fundamental for processes of cellular respiration, cellular utilization of oxygen, DNA and RNA reproduction, maintenance of cell membrane integrity, and sequestration of free radicals.[17]

Cocoa flavonoids have unique antioxidant properties with skin health benefits. In addition to containing (−)-epicatechin, (+)-catechin, and procyanidins, cocoa and chocolate contain other flavonoids, including other catechins and the flavonol quercetin and its glycosides.[18]

In one study, researchers analyzed 2 groups of women who consumed either a high amount of flavonol (326 mg/d) cocoa powder or a low amount of flavonol (27 mg/d) cocoa powder dissolved in 100 mL water for 12 weeks. Evaluation of the skin surface in participants in the high cocoa flavonol group showed a decrease in skin roughness and scaling compared to participants in the low cocoa flavonol group at week 12. Researchers concluded that dietary flavonols from cocoa contribute to endogenous photoprotection, improve dermal blood circulation, and affect cosmetically relevant skin surface and hydration variables.[19]

Neukam et al[20] investigated the acute effects of a single dose of cocoa rich in flavonols on dermal microcirculation. In a crossover design study, healthy women ingested a cocoa drink (100 mL) with high (329 mg) or low (27 mg) content of cocoa flavonols. The primary flavonol monomer in both drinks was epicatechin. Results of the study showed that ingestion of the flavonol-rich cocoa acutely increased dermal blood flow and oxygen saturation.[20]

Marine fish oils, particularly those rich in eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) are the 2 most studied fish oils that have been shown to exhibit strong anti-inflammatory effects on the skin. In patients with atopic dermatitis, changes in the metabolism of eicosanoids with increased quantities of the AA-derived lipoxygenase products have been observed. Free EPA may compete with AA, resulting in an anti-inflammatory effect.[21]

In one trial, 20 participants hospitalized for acute guttate psoriasis, completed a 10-day trial in which they were randomly allocated to receive daily infusions with either an omega-3 fatty acid–based lipid emulsion (EPA 2.1 g + DHA 21g/100 mL) or a conventional omega-6 lipid emulsion (EPA+DHA<0.1 g/100 mL). Although moderate improvements were found in the omega-6 group, the severity of disease markedly decreased in all

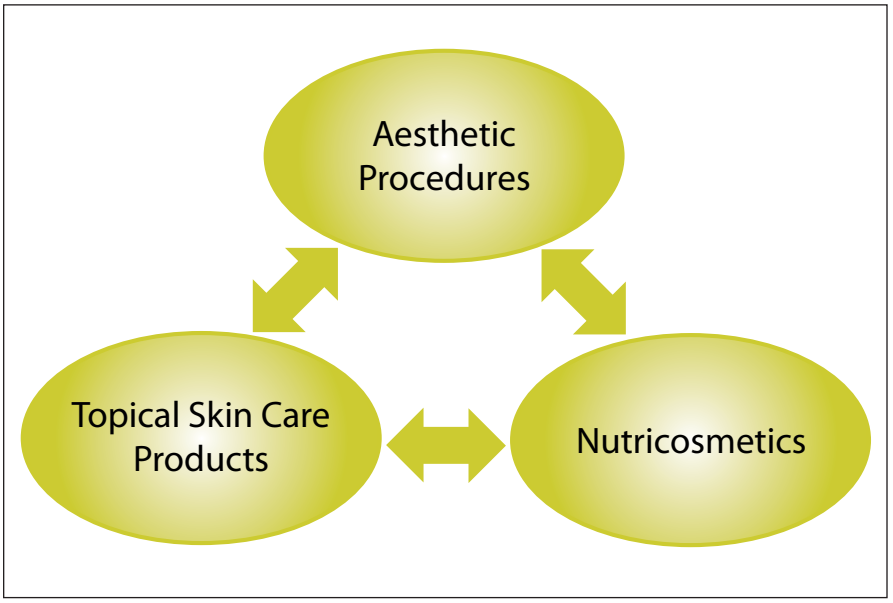

Figure 3. Nutricosmetics provide active nutritional ingredients that can be used in conjunction with topical skin care products and aesthetic procedures to promote healthy skin.

participants of the omega-3 group, with improvements in all score systems ranging between 45% and 76% within 10 days ($P<.05$ for each variable). Researchers concluded that modulation of eicosanoid (eg, EPA) metabolism by intravenous omega-3 fatty acid supplementation exerted a rapid beneficial effect on inflammatory skin lesions in acute guttate psoriasis.[34]

COMMENT

As the effects of aging are so manifest in the appearance, structure, mechanics, and barrier function of the skin, it is not surprising that much effort has been made in research to better understand them. To work effectively, nutricosmetics should include the key antioxidants found in the free radical–detoxifying enzymes glutathione peroxidase and SOD. GliSODin offers a bioavailable source of SOD, while cartenoids and cocoa flavonoids can provide added antioxidant protection against oxidative stress. Selenium, zinc, copper, and molybdenum are cofactors in many pathways that promote the production of glutathione peroxidise and protect against oxidative cellular injury. Incorporating these critical nutrients may help to prevent antioxidant deficiency with resulting protection of mitochondria against premature oxidative damage and cellular aging. Therefore, the administration under professional advice of synergistic combinations of some of the above mentioned antioxidants in the diet as well as topically (for skin protection) may have favorable effects on the skin and overall health, especially for individuals with high levels of oxidative stress and individuals who do not consume a healthy diet that includes 5 rations of fresh fruit and vegetables daily (Figure 3).[35,36]

CONCLUSION

For many years in Europe and Japan, consumers have embraced the concept of "beauty from the inside out" and the idea of nutricosmetics. Topical cosmeceutical products have dominated the market for years, but consumers are increasingly looking for oral antioxidant supplements that support a healthy lifestyle and healthy physical appearance.

By combining nutricosmetics with topical skin care products and aesthetic procedures, patients will receive all parameters required to optimize skin health and reduce oxidative stressors, a primary accelerator to skin aging. Nutricosmetics essentially are the missing link to medical aesthetic programs.

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