The cosmeceutical realm

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Abstract The cosmeceutical realm is composed of functional cosmetics designed to adorn face and body without changing the structure of the human form. Although this may seem confusing, indeed cosmeceuticals have never been well defined. Cosmeceuticals developed for facial application typically claim to induce more even skin tone, improve skin texture, increase skin radiance, decrease the appearance of skin wrinkling, and provide antiaging benefits. Nondrug active ingredients are usually incorporated into moisturizing vehicles designed to accomplish the aforementioned claims. There is no doubt that cosmeceuticals represent the most rapidly expanding frontier in dermatology.

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Introduction

The realm of cosmeceuticals is rapidly expanding. This expansion is due to the availability of new ingredients, the financial rewards for developing successful products, consumer demand, and a better understanding of skin physiology. Thus, the cosmeceutical realm combines the skills of the cosmetic formulator, the ingenuity of the marketing expert, the desires of aging population, and the knowledge of the dermatologist into one bottle sitting on the shelf of the store for purchase. How exactly did the concept of cosmeceuticals arise? Perhaps a quick review of the history of appearance-related products would be useful.

History of appearance-related products

The modern concept of improving appearance through a product purchased for adornment was the beauty patch. The beauty patch was developed around 1600 in Europe to cover permanent facial scars present on smallpox epidemic survivors. The patches consisted of black silk- or velvet star-, moon-, and heart-shaped pieces that were carefully placed on the face and stored in shallow metal boxes with a mirror in the cover, known as a patch box. The portability of the adornment was important because a replacement was necessary should a patch fall off in public. The wearing of patch adornment evolved into an unspoken language: a patch near a woman’s mouth signaled flirtatiousness, a patch on a woman’s right cheek indicated she was married, a patch at the corner of a woman’s eye announced smoldering passion, and so on. The development of the smallpox vaccine eliminated the need for the patch adornment, but the portable cosmetic was born and eventually evolved in the modern compact used for the application of facial powder and facial foundation.1

The first step in the history of modern adornment was the compact, but the second development was the concept of applying a colored cosmetic to the entire face. The concept of applying powder to the face was replaced with the first successful liquid cosmetic known as “wet white” or “French White,” which consisted of face powder suspended in a liquid vehicle.2 This was considered an improvement over simply powdering the skin due to superior adherence
and product longevity. Later, “grease paints” were developed as pigments and fillers suspended in oily vehicles. These products were difficult to wear and apply for individuals outside the theater. Before this time, adornment was mainly practiced by actors and actresses to improve their stage appearance.

The first breakthrough in facial cosmetic adornments for the mass market occurred when Max Factor developed cake makeup, which he patented in 1936. This product provided excellent coverage, a velvety look and added facial color. Since that time, the number of facial adornments has increased dramatically to include blush, lipstick, eye shadow, eyeliner, eyebrow pencil, mascara, and so on. These colored cosmetics, however, simply improved the visual appearance of the skin and offered no long-lasting effects.

The development of medical science and cosmetic ingredient technology paved the way for a new type of adornment product known as functional cosmetic. Functional cosmetics encompass the realms of the original colored cosmetics but also include cosmeceuticals and neurocosmeceuticals. Both of these categories aim for the same goal: improving senescence of the skin and mind. The modern consumer demands more than just temporary adornment. The consumer is Internet savvy, searching the medical archives for ingredients that will make her or his skin perform better rather than just looking better. The consumer wants to look younger, think younger, and act younger. Thus, the challenge for the appearance industry is to deliver on consumer desires, either with reality or promises.

A subgroup of functional cosmetics has been recently termed neurocosmeceuticals. These are topical agents applied to the skin to induce a feeling of well-being, playing into the philosophical concept of the mind-body connection. There are those who believe that the skin cannot appear healthy unless the mind is content. Furthermore, the health of the mind can be improved through the skin. Neurocosmeceuticals claim to improve well-being by altering neurotransmitters through topical applications. Indeed, ingredients have been identified that inhibit the release of substance P and enhance the release of β-endorphins.

The expectation is that cosmeceuticals will extend beyond cosmetics to enhance functioning, attempting to return the structure to a more youthful state; for example, wrinkle-reducing moisturizers, nail growth serums, and skin lightening creams. The term cosmeceutical is somewhat confusing, however, as both prescription and over-the-counter products have been labeled by this word. Drug cosmeceuticals include topical retinoids for improving dermal collagen production, topical minoxidil for enhanced scalp hair growth, and efflorescent for facial hair growth reduction. These products will not be discussed because they are not available to the consumer except by prescription. The second category of cosmeceuticals includes over-the-counter drugs, such as sunscreens and antiperspirants, which will not be discussed. This article focuses on those ingredients currently dominating the cosmeceutical realm that are considered functional cosmetics.

### Functional cosmetics

Although the cosmeceutical market may be vast and confusing, it is possible to simplify our discussion by organizing cosmeceutical ingredients by their ability to deliver on marketing claims. There are only so many consumer-appealing words that can be used to attractively describe the skin. The major terms used to describe the effect of cosmeceuticals on the skin are listed in Table 1. This article examines how ingredients contained within the cosmeceutical formulation attempt to deliver of these specific claims.

### More even skin tone

The claim “more even skin tone” implies that the skin does not contain areas of hypo- and hyperpigmentation. Because there is no currently available cosmeceutical formulation for the treatment of hypopigmentation, all of the products in this category are aimed at skin lightening for hyperpigmented skin. The gold standard for hyperpigmentation therapy in the United States was hydroquinone until recently, when the Food and Drug Administration announced that hydroquinone was no longer considered safe. This meant that all over-the-counter 2% or less hydroquinone formulations could no longer be sold. Concern arose because oral hydroquinone has been reported to cause cancer in mice fed with large amounts of the substance. Although oral consumption probably is not related to topical application, hydroquinone remains controversial because it actually is toxic to melanocytes.

Hydroquinone, a phenolic compound chemically known as 1,4-dihydroxybenzene, functions by inhibiting the enzymatic oxidation of tyrosine and phenol oxidases. It covalently binds to histidine or interacts with copper at the active site of tyrosinase. It also inhibits RNA and DNA synthesis and may alter melanosome formation, thus selectively damaging melanocytes. These activities suppress the melanocyte metabolic processes inducing gradual decrease of melanin pigment production. This has led to an industry search for the next cosmeceutical lightening ingredient. Some of the most popular skin lightening ingredients are discussed next.

### Azelaic acid

Azelaic acid is one of the ingredients that may take the place of hydroquinone in pigmentation cosmeceuticals. It is a 9-carbon dicarboxylic acid obtained from cultures of **Table 1** Marketing cosmeceutical descriptions

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Pityrosporum ovale. Although its pigment lightening effects are mild, several large studies done with a diverse ethnic background population have compared its efficacy to that of hydroquinone.\(^5,6\) It also interferes with tyrosinase activity but additionally interferes with DNA synthesis. It appears to have specificity for abnormal melanocytes and, thus, it may be able to prevent lentigo maligna; but this claim would not be appropriate in the cosmeceutical realm.

Licorice extract

Licorice extracts are found in cosmeceuticals to decrease facial redness and reduce pigmentation. The extract contains liquiritin and isoliquertin, which are glycosides containing flavonoids,\(^7\) that induce skin lightening by dispersing melanin. Liquiritin must be applied in the dose of 1 g/d for 4 weeks to see clinical results, but irritation is not frequently seen. Unfortunately, it is a weak skin lightening agent and must be combined with other ingredients for good clinical results.

Kojic acid

Kojic acid, chemically known as 5-hydroxymethyl-4H-pyrane-4-one, is one of the most popular cosmeceutical skin lightening agents found in cosmetic-counter skin lightening cream distributed worldwide. It is a hydrophilic fungal derivative obtained from Aspergillus and Penicillium species.\(^8\) It used to be the most popular agent used in Japan for the treatment of melasma, but it has recently been banned because of its sensitizing abilities. Some studies indicate that kojic acid is equivalent to hydroquinone in pigment lightening ability.\(^9\) The activity of kojic acid is attributed to its ability to prevent tyrosinase activity by binding to copper.

Aloesin

Aloesin is a low-molecular-weight glycoprotein obtained from the aloe vera plant. It is a natural hydroxymethylchro- mone that functions by competitive inhibition of tyrosinase at the DOPA oxidation site.\(^10,11\) In contrast to hydroquinone, it shows no cell cytotoxicity; however, it has a limited ability to penetrate the skin because of its hydrophilic nature. It is sometimes mixed with arbutin to enhance its skin lightening abilities.

Arbutin

Arbutin is obtained from the leaves of the Vaccinium vitis- idaea and other related plants. It is a naturally occurring glucosylpyranoside that causes decreased tyrosinase activity without affecting messenger RNA expression.\(^12\) It also inhibits melanosome maturation. Arbutin is not toxic to melanocytes, and in Japan it is used in a variety of pigment lightening preparations at concentrations of 3%. Higher concentrations are more efficacious than lower concentrations, but a paradoxical pigment darkening may occur. A more effective form, known as deoxyarbutin, has been developed that may enhance the pigment lightening abilities of this cosmeceutical.\(^13\)

Improved skin texture

Many cosmeceuticals claim to improve skin texture, which is a rather ambiguous term without true scientific meaning. Skin texture might be loosely interpreted to mean the contour and regularity of the skin surface. The texture can be improved through the use of exfoliants that remove dead skin scale or through the use of agents that activate receptors resulting in more normalized keratinization. Exfoliants, such as glycolic acid, lactic acid, gluconolactone, ferrulic acid, or lactobionic acid, function to chemically dissolve the bridges between desquamating keratinocytes. This speeds the removal of skin scale from the surface and creates cosmetically improved skin texture. The skin texture, however, can also be improved through the activation of retinoid receptors.

Cell surface retinoid receptors can be modulated to improve the appearance of aging skin.\(^14\) Prescription retinoids, such as tazarotene and tretinoin, are well studied for their ability to induce the skin changes; however, over-the-counter retinoids may demonstrate some of the same effects, to a lesser degree.\(^15,16\) It is theoretically possible to interconvert the retinoids from one form to another. For example, retinyl palmitate and retinyl propionate, chemically known as retinyl esters, can become biologically active after cutaneous enzymatic cleavage of the ester bond and subsequent conversion to retinol. Retinol is the naturally occurring vitamin A form found in red, yellow, and orange fruits and vegetables. It is the pigment responsible for vision, but it is highly unstable. Retinol can be oxidized to retinaldehyde and then oxidized to retinoic acid, also known as prescription tretinoin. It is this cutaneous conversion of retinol to retinoic acid that is responsible for the biologic activity of some of the new stabilized over-the-counter vitamin A preparations designed to improve the appearance of benign photodamaged skin.\(^17\) Unfortunately, only small amounts of retinyl palmitate and retinol can be converted by the skin, accounting for the increased efficacy seen with prescription preparations containing retinoic acid.

The main problem with prescription retinoids is their irritability. Unfortunately, as the biologic efficacy of the retinoid increases, so does the irritability. This is also the case with the over-the-counter retinoids. Retinol is more irritating than the retinyl esters and also more unstable. It is for this reason that in cosmeceutical formulations, which may not be manufactured under strict oxygen-devoid conditions, it is preferred to add retinyl palmitate to moisturizing creams. The retinyl palmitate, however, may not be added for its activation of the retinoid receptor. Retinyl palmitate is a potent anti-
oxidant and humectant. It is this multifunctionality that makes retinoids popular in cosmeceutical antiaging formulations.

**Increased skin radiance**

Skin radiance is not a dermatologically relevant term and it is thus hard to characterize, yet it is probably the most popular marketing term in the current marketplace. Radiance probably is a combination of the overall appearance of the skin, but it is best related to the reflection of light from the skin surface. The skin surface can be modified through a variety of techniques, but those ingredients that accompany radiance-improving claims alter the optics of the skin surface. Substances that can modify skin optics include film-forming proteins and light-reflective pigments.

Proteins formed the basis of the earliest moisturizers. They were produced by boiling cow skin and added as thickeners. As cosmetic science has evolved, increasingly complex uses for peptides, which form the building blocks of proteins, have appeared. One cosmeceutical use of peptides is as a carrier for larger-molecular-weight molecules to enhance penetration. For example, copper, a known cofactor in the production of collagen during wound healing, was linked to a peptide to enhance penetration in the wounded skin. This copper peptide technology was then adapted to general skin care as an antiaging moisturizer in both the physician dispensed and mass markets.

Probably the newest use of peptides is as regulators of cellular function. Because the body uses peptides to communicate between cells, it was theorized that perhaps engineered peptides might be able to up-regulate or down-regulate cutaneous functions that had decayed with time due to the cumulative effects of aging. Probably the most widely distributed cosmeceutical peptide is a pentapeptide composed of lysine, threonine, threonine, lysine, and serine, known as KTTKS. The KTTKS peptide was linked to palmitic acid to enhance penetration. Thus, the commercialized pentapeptide is termed Pal-KTTKS with the trade name Matrixyl (Sederma, France). Matrixyl contains 800 parts per million of Pal-KTTKS, which is typically used at a concentration of 1 to 4 parts per million in currently marketed cosmeceutical moisturizers.

The exact mechanism of action of Pal-KTTKS has not been fully elucidated, but it is known that this pentapeptide is a fragment of collagen type I. Many different fragments of collagen type I were studied, but Pal-KTTKS showed the best in vitro biologic response in fibroblast subconfluent monolayer cultures. It is thought that the exposure of fibroblasts to high levels of collagen type I breakdown products triggers a cellular recognition that too much collagen has been destroyed. This in turn down-regulates the activity of collagenase resulting in less collagen destruction and enhanced collagen synthesis. Although this has never been demonstrated in human clinical studies, there is no doubt that proteins can improve the appearance of the skin.

Proteins can form a film over the skin surface impeding transepidermal water loss and increasing the smoothness of skin surface. This combination of better moisturization and surface evenness produces an immediate improvement in skin appearance, accounting for the popularity of sophisticated peptides and generic bovine collagen. The light-reflective capabilities of the skin can also be improved through the topical application of fish scale essence, mica, and bismuth oxychloride. These ground particulates reflect light producing a more vibrant facial appearance while camouflaging facial wrinkles, our next cosmeceutical claim for evaluation. Of course, all of the effects are temporary until the material is removed from the skin surface.

**Decreased appearance of skin wrinkling**

The most commonly made claim in the cosmeceutical realm is “decreased appearance of skin wrinkling.” Although “decreasing wrinkles” is a drug claim, “decreasing the appearance of wrinkles” is a cosmetic claim. This is an important distinction. What exactly does “decreasing the appearance of wrinkles” mean from a scientific standpoint? It means moisturizing the skin. The easiest wrinkles to improve are those of skin dehydration. Moisturizers can smooth down desquamating corneocytes and fill in the gaps between the remaining corneocytes to create the impression of tactile smoothness. This effect is temporary, of course, until the moisturizer is removed from the skin surface by wiping or cleansing. From a functional standpoint, moisturizers can create an optimal environment for healing and minimize the appearance of lines of dehydration by decreasing transepidermal water loss. Transepidermal water loss increases when the brick and mortar organization of the protein-rich corneocytes held together by intercellular lipids is damaged.

There are 3 cosmeceutical ingredient categories that can reduce transepidermal water loss: occlusives, humectants, and hydrophilic matrices. The most common method for reducing transepidermal water loss is the application of an occlusive ingredient to the skin surface. These are basically oily substances that create a barrier to water evaporation. The most effective occlusive ingredient is petrolatum, which blocks 99% of water loss from the skin surface. It is the gold standard to which all other moisturizers are compared. Its bad smell, sticky feel, and ability to stain clothing, however, has lead to the use of other occlusive agents, including dimethicone, mineral oil, vegetable oils, waxes, and lanolin. The prevention of water loss from the skin surface due to a damaged barrier by occlusive moisturizing ingredients leads to improvement in the fine lines of dehydration especially apparent around the eyes.

Another concept in rehydrating the stratum corneum and decreasing fine wrinkling is the use of humectants. Humectants are substances applied to the skin surface that attract and hold water, much like a sponge. Substances that function as humectants include glycerin, honey, sodium lactate, urea,
propylene glycol, sorbitol, pyrrolidone carboxylic acid, gelatin, hyaluronic acid, vitamins, and some proteins.\(^{19,21}\) Humectants combined with occlusives are the most effective method of immediately reducing the appearance of fine facial wrinkles, meaning that moisturizing properties are used to substantiate most product-related antiaging claims.

Wrinkles can also be reduced through the use of film forming agents, which are known as hydrophilic matrices. Proteins were discussed previously as effective film-forming agents and thus can be classified as hydrophilic matrix moisturizers. These large-molecular-weight substances create a film over the skin surface, thereby retarding water evaporation. The first hydrophilic matrix developed was an oatmeal bath. The colloidal oatmeal created a film that prevented water from leaving the skin to enter the bath water. Hyaluronic acid is a newer hydrophilic matrix moisturizer used in many antiaging cosmeceutical moisturizers.

Enhanced antiaging skin benefits

This article has discussed many different technologies used in antiaging cosmeceuticals. Many of these claims have been of a truly cosmetic nature. One claim that is frequently made on product packaging is “enhanced antiaging skin benefits.” Although this may at first seem to be a rather empty phrase, in many cases it is the incorporation of sunscreens into cosmetic formulations that support this claim. The moisturization effects of the cosmeceutical are perceived within a matter of hours as the skin feels softer and looks shinier, but the antiaging claims related to photoprotection take years to manifest. Yet, sunscreen actives that provide broad-spectrum photoprotection in the UV-A wavelengths are some of the most effective antiaging ingredients. The ingredients include benzophenone, benzophenone complexes, avobenzone, and ecamsule.

**Benzophenone**

The benzophenone family of sunscreens provides protection primarily in the UV-A range of lower than 320 nm. The 3 sunscreens in the benzophenone family are oxybenzone, dioxybenzone, and sulisobenzone. Only oxybenzone is approved for use in United States and provides weak UV-A photoprotection for less than 320 nm. It is a thick oil that can make sunscreen-containing moisturizers feel sticky if used in high concentration. For this reason, oxybenzone has found a new importance in cosmeceuticals for its ability to stabilize avobenzone, an important UV-A photoprotectant.

**Avobenzone**

Avobenzone, also known as Parsol 1789, was an important step forward in UV-A photoprotection and antiaging. Unfortunately, it is photoinstable. It is estimated that all of the avobenzone in a sunscreen-containing moisturizer is photoinactivated 5 hours after sun exposure, which corresponds to 50 J of light energy. Avobenzone, however, has assumed new importance in a proprietary sunscreen complex, known as Helioplex (Neutrogena, Los Angeles, Calif), which combines avobenzone with oxybenzone and 2,6-diethylhexylnaphthalate (Hallbrite TQ, Syms- rise, Germany) to create a photostable avobenzone with long-lasting UV-A photoprotectant qualities. Photostable UV-A organic filters are frequently used to substantiate antiaging cosmeceutical claims.

**Ecamsule**

The newest ingredient to be added to the US sunscreen monograph is ecamsule, better known as Mexoryl (L’Oreal, France). Ecamsule was originally developed to stabilize avobenzone, much like Helioplex (Neutrogena) discussed earlier. It certainly will find its way into antiaging cosmeceuticals to provide long-lasting UV-A photoprotection because UV-A radiation is the prime driver of premature photoaging.

**Conclusions**

Cosmeceuticals form an important part of the skin treatment market. The dermatologist may wonder why cosmeceuticals are not more thoroughly studied and tested. This is in part because it may be in the manufacturer’s best interest not to fully understand exactly what a cosmeceutical active can accomplish. Cosmeceuticals that function too well would alter the structure and function of the skin and become drugs. The current state of the cosmeceutical marketplace is due to the ambiguous nature of this category. Consumers want products that function, yet these products are not drugs, but cosmetics. At this writing, cosmeceuticals can improve the appearance of the skin. Claims such as more even skin tone, improved skin texture, increased skin radiance, decreased appearance of skin wrinkling, and enhanced antiaging benefits are frequently made based on a variety of ingredients reviewed in this article.

**References**