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Anti-aging Skin Care Formulations

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INTRODUCTION

There are many cosmetic materials that are claimed to have anti-aging effects when used topically. Since there are so many of these materials and since the term anti-aging is very broad (in terms of prevention vs. improvement and the wide array of possible benefit areas such as wrinkling, sagging, texture, sallowness, hyperpigmentation, etc.), this relatively short chapter must necessarily be selective in its scope. Thus, this discussion will focus on only a few classes of cosmetic agents which are reported to have bio-activity to provide wrinkling and/or sagging improvement (i.e., repair or reversal). Particular attention will be directed to those materials within these classes for which there are readily available or published clinical data to support their reported skin appearance improvement benefits.

VITAMIN A

Forms

There are several forms of vitamin A that are used cosmetically. The most widely utilized ones include retinol, retinyl esters (e.g., retinyl acetate, retinyl propionate, and retinyl palmitate), and retinaldehyde. Through endogenous enzymatic reactions, all of these are converted ultimately to trans-retinoic acid (trans-RA), which is the active form of vitamin A in skin. Specifically, retinyl esters are converted to retinol via esterases. Retinol is then converted to retinaldehyde by retinol dehydrogenase. And finally retinaldehyde is oxidized to RA by retinaldehyde oxidase.

Mechanisms

Since trans-RA is the active form of vitamin A in skin, the abundant published literature on the former is applicable to this discussion. Trans-RA interacts with nuclear receptor proteins described as RA receptors and retinoid X receptors, which can form heterodimer complexes. These complexes then interact with specific DNA sequences to affect transcription, to either increase or decrease expression of specific proteins/enzymes (1). Using genomic methodology, we have observed that the expression of over 1200 genes is

significantly affected by topical retinoid treatment of photoaged human skin (unpublished observations). Many of these changes can be ascribed, at least on some level, as being normalization of the altered skin conditions that occur with aging (induced by both chronological and environmental influences such as chronic sun exposure). Some specific changes induced by retinoid that are likely relevant to skin anti-wrinkle benefits are those that result in thicker skin to diminish the appearance of fine lines and wrinkles, e.g., increased epidermal proliferation and differentiation (increased epidermal thickness), increased production of epidermal ground substance [glycosaminoglycans (GAGs) which bind water, increasing epidermal hydration and thickness], and increased dermal production of extracellular matrix components such as collagen (increase dermal thickness) (2).

In addition to stimulation of events in skin such as those mentioned above, retinoids can also have an inhibitory effect on other tissue components. For example, retinoids are reported to inhibit production of collagenase (3). And while retinoid will stimulate production of ground substance (GAGs) in epidermis, it will inhibit production of excess ground substance in photoaged dermis (Fig. 1). While a low level of GAGs are required in the dermis for normal collagen structure and function, excess dermal GAGs are associated with altered dermal collagen structure and wrinkled skin appearance in photoaged skin (4) and in the Shar Pei dog (5). Reduction in this excess is associated with reduced skin wrinkling (6,7).

Since at least some of the epidermal effects of topical retinoid (e.g., epidermal thickening) (8) occur relatively rapidly (days) after initiation of treatment, some skin benefits (e.g., diminution of fine lines) can be realized quickly. The dermal effects likely occur on a much longer time frame (weeks to months) such that reduction in skin problems like wrinkles require much longer time frames (weeks to months) (2).

Efficacy

While much of the substantial literature on the improvement of skin wrinkles by topical retinoids is focused on trans-RA, there are also data available on the vitamin A compounds which are used cosmetically. Since retinoids are irritating to skin, defining skin-tolerated doses clinically is a key step in working effectively with these materials. Retinol is better

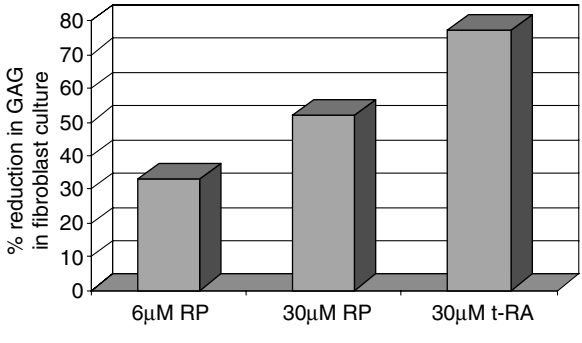

Figure 1 Retinoids reduce excess dermal GAGs. In cell culture, using fibroblasts from an old donor (57 years old), there was a two- to three-fold increase in GAGs (measured as hyaluronic acid) versus from a young donor (neonatal). The treatments were effective in reducing the excess GAG level. *Abbreviations*: RP, retinyl propionate; t-RA, trans-retinoic acid.

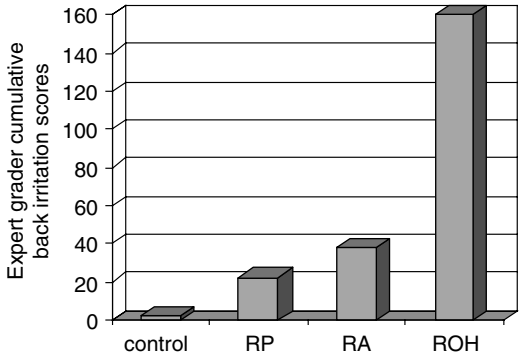

Figure 2 Retinoid irritation in cumulative human back irritation testing (double-blind, vehicle-controlled, randomized study; daily patching for 20 days, under semi-occluded patch, n = 45; 0–3 irritation grading). Doses and abbreviations used are: 0.09% RP (retinyl propionate), 0.086% RA (retinyl acetate), and 0.075% ROH (retinol). RP and RA were significantly less irritating than ROH, and RP was less irritating than RA.

tolerated by the skin than trans-RA (2). In our testing we noted that retinyl propionate is milder to skin than retinol and retinyl acetate (Fig. 2).

Since retinoids in general tend to be fairly potent, topical doses of less than 1% are generally sufficient to obtain significant effects. At low doses, in double-blind, split-face, placebo-controlled facial testing (12-week duration), both retinol and retinyl propionate have been shown to be significantly effective in reducing facial hyperpigmentation and wrinkles across the study (Fig. 3). Determination of treatment effects was based on quantitative computer image analysis and blinded expert grading of high resolution digital images.

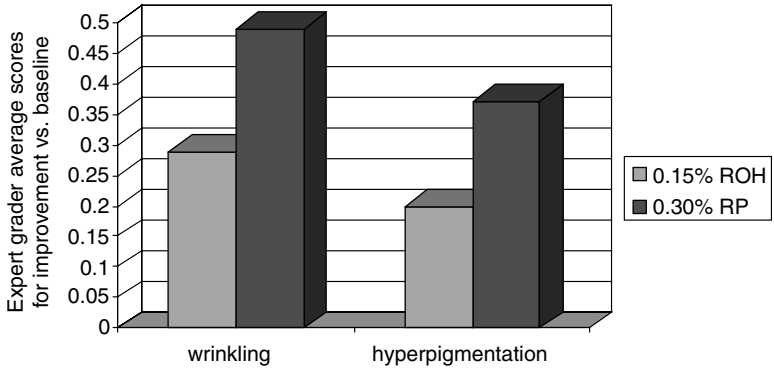

Figure 3 Reduction in wrinkles and hyperpigmentation in a 12-week clinical study (double-blind, left-right randomized, split-face, placebo vehicle-controlled study with once daily application, n = 52–56 per product). Evaluation for reduction versus baseline in wrinkling and hyperpigmentation was done by three independent expert graders (0–4 grading scale) on blind-coded images after four, eight, and 12 weeks of treatment. The grader scores at each time point were averaged. There were significant effects for both treatments across the study. The data presented here are averages for all three time points. The low irritation of RP permits use of higher levels to achieve greater effects without significant negative aesthetic issues.

There are also clinical studies published on other retinoids. Retinyl palmitate has very low irritation potential and is effective if tested at a very high dose such as 2% (9). There are also several references describing the clinical efficacy of retinaldehyde, typically at a dose of 0.05% (10–12). However, retinaldehyde has irritation potential similar to retinol (13).

Product/Formulation Challenges

There are two primary challenges in working with retinoids. One is their tendency to induce skin irritation (as noted above) which negatively affects skin barrier properties. While high doses will provide ever greater skin aging improvement, the associated irritation tends to define an upper concentration limit where they can be used practically. While the skin may have some capacity to accommodate to retinoid treatment to yield less irritation, it is not completely eliminated even with long-term use, as demonstrated by evaluation of skin barrier function (Fig. 4). Mitigation of the irritation may be managed to some extent with appropriate formulation to meter delivery into the skin, use of retinyl esters which are less irritating than retinol (as noted above), or inclusion of other ingredients (e.g., those with anti-inflammatory activity) to counter this issue.

The second key issue is instability, especially to oxygen and light. Thus, to ensure stability of retinoid in the finished product, formulation and packaging must be done in an environment that minimizes exposure to oxygen and light. The final product packaging also ideally needs to be opaque and oxygen impermeable, including use of a small package orifice to reduce oxygen exposure once the container is opened. In addition, a variety of other strategies can be employed, e.g., encapsulation of the retinoid and inclusion of stabilizing antioxidants.

VITAMIN B3

Forms

There are three primary forms of vitamin B3 that have found utility in skin care products: niacinamide (*aka* nicotinamide), nicotinic acid, and nicotinate esters (e.g., myristoyl nicotinate, benzyl nicotinate).

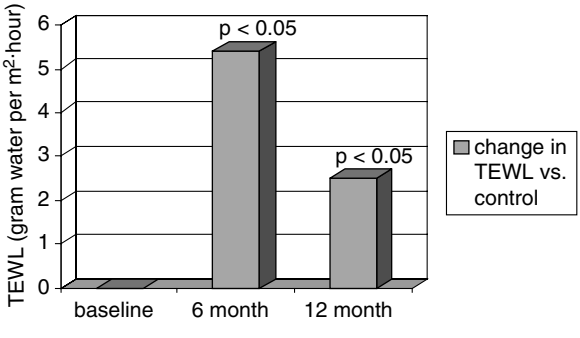

Figure 4 Effect of topical 0.05% trans-retinoic acid on skin barrier as determined by transepidermal water loss (TEWL). Although the skin becomes more tolerant of topical retinoic acid, even after 12 months of treatment there is still significant elevation of TEWL above baseline.

Mechanisms

Vitamin B3 serves as a precursor to a family of endogenous enzyme co-factors, specifically nicotinamide adenine dinucleotide (NAD), its phosphorylated derivative (NADP), and their reduced forms (NADH, NADPH), which have antioxidant properties. These co-factors are involved in many enzymatic reactions in the skin, and thus have potential to influence many skin processes (14). This precursor role of vitamin B3 may thus be the mechanistic basis for the diversity of clinical effects observed for a material such as niacinamide. While precisely how the dinucleotide co-factors might contribute to all these effects has not been elucidated, several specific actions of niacinamide have been described (14–19). For example, topical niacinamide has the following effects:

- Niacinamide inhibits sebum production, specifically affecting the content of triglycerides and fatty acids. This may contribute to the observed reduction in skin pore size and thus improved skin texture (a component of texture being enlarged pores).
- Niacinamide increases epidermal production of skin barrier lipids (e.g., ceramides) and also skin barrier layer proteins and their precursors (keratin, involucrin, filaggrin), leading to the observed enhancement of barrier function as determined by reduced transepidermal water loss (TEWL). This improved barrier also increases skin resistance to environmental insult from damaging agents such as surfactant and solvent, leading to less irritation, inflammation, and skin redness (e.g., facial red blotchiness). Since inflammation is involved in development of skin aging problems, the barrier improvement may contribute to the anti-aging effects of topical niacinamide. The anti-inflammatory and sebum reduction effects of niacinamide likely contribute to the anti-acne effect reported for this material (20).
- Niacinamide and its metabolite 1-methyl nicotinate have been reported (21,22) to have anti-inflammatory properties (e.g., inhibition of inflammatory cytokines).
- Niacinamide increases production of collagen which may contribute to the observed reduction in the appearance of skin wrinkling.
- Niacinamide reduces the production of excess dermal GAGs (glycosaminoglycans). In cell culture testing, as noted above for retinyl propionate, 0.5 mM niacinamide reduced excess GAG production by 15%.
- Niacinamide inhibits melanosome transfer from melanocytes to keratinocytes, leading to reduction in skin hyperpigmentation (e.g., hyperpigmented spots).
- Niacinamide inhibits skin yellowing. A contributing factor to yellowing is protein oxidation (glycation; Maillard reaction), which is a spontaneous oxidative reaction between protein and sugar (23–25), resulting in cross-linked proteins (Amedori products) that are yellow-brown in color. These products accumulate in matrix components such as collagen that have long biological half-lives (26,27). Niacinamide has been separately reported (28,29) to have anti-glycation effects.

Since nicotinic acid and its esters are also precursors to NAD(P), they would be expected to provide these same benefits to skin. Nicotinic acid and many (if not all) of its esters (following in-skin hydrolysis to free nicotinic acid) also stimulate blood flow, leading to increased skin redness or a flush response (30).

Efficacy

As representative for the vitamin B3 family of compounds, there are several published reports on the diversity of clinical effects of topical niacinamide (14–18). These data

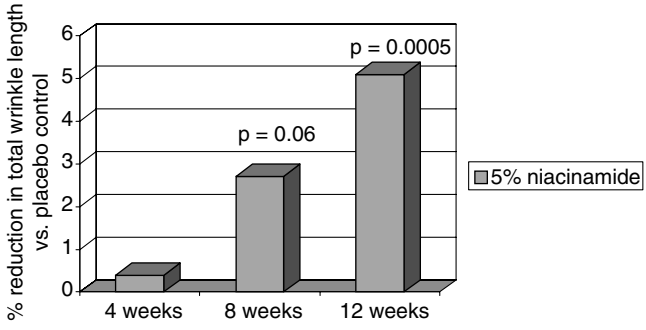

Figure 5 Topical 5% niacinamide reduces fine lines/wrinkling in facial skin. Subjects were female Caucasians (n = 50) who applied placebo control versus 5% niacinamide formulations to their faces (12-week, double-blind, split-face, left-right randomized clinical trial).

were obtained from double-blind, placebo-controlled, left-right randomized studies. For example, topical niacinamide has been shown to reduce skin fine lines/wrinkling (Fig. 5). The effect increases over time and is significant after eight to 12 weeks of treatment. Topical niacinamide also improves other aspects of aging skin, such as reduction in sebaceous lipids (oil control) and pore size, which likely contribute at least in part to improved skin texture (Fig. 6). Additionally, niacinamide improves skin elastic properties as demonstrated for two parameters of skin elasticity (Fig. 7). Beyond these effects, there is also improvement in appearance of skin color (reduction in hyperpigmented spots and reduced skin yellowing) as noted above. Fairly high doses (2–5%) of vitamin B3 have been used to achieve desired benefits. However, since there is very high tolerance of the skin to niacinamide even with chronic usage, high doses can be used acceptably. In fact, as noted above, since topical niacinamide improves skin barrier, it actually increases the skin's resistance to environmental insult (e.g., from surfactant) and reduces red blotchiness (Fig. 8).

Some data on myristoyl-nicotinate have been presented (31) to suggest that a similar broad array of benefits occurs with this agent when used topically (1–5% doses). Clinical data for topical nicotinic acid and other esters are not available.

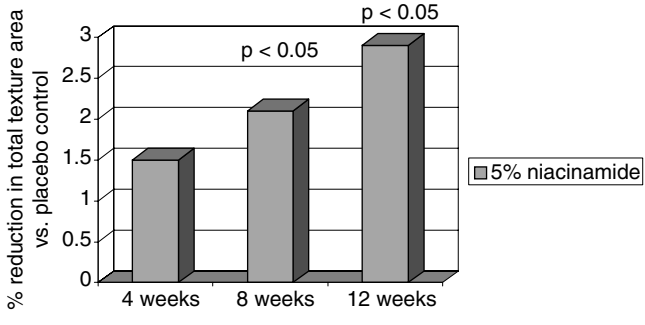

Figure 6 Topical niacinamide improves skin surface texture. Subjects were female Caucasians (n = 50) who applied placebo control versus 5% niacinamide formulations to their faces (12-week, double-blind, split-face, left-right randomized clinical trial).

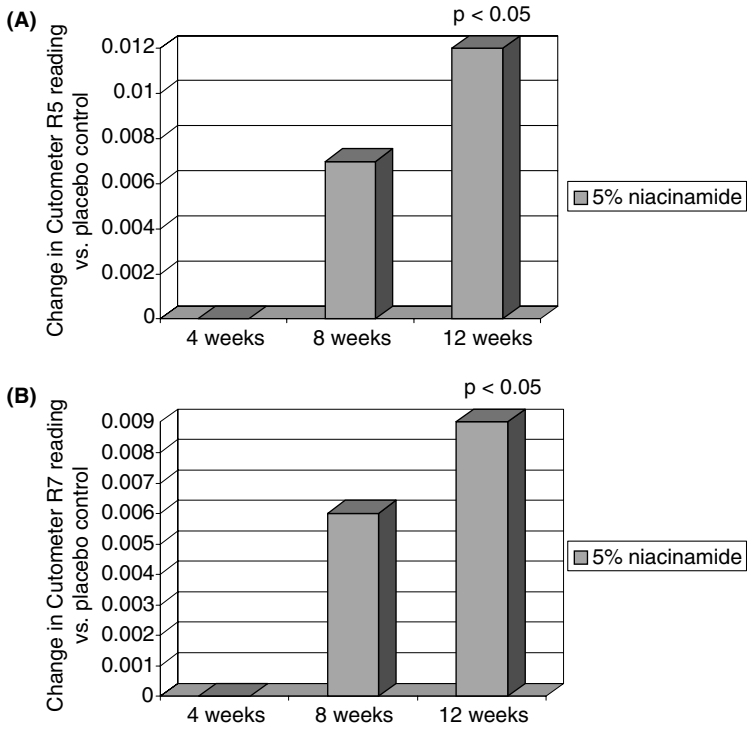

Figure 7 Topical 5% niacinamide improves skin elasticity. Subjects were female Caucasians (n = 50) who applied placebo control versus 5% niacinamide formulations to their faces (12-week, double-blind, split-face, left-right randomized clinical trial). (**A**) Effect on R5 parameter (measure of viscoelastic properties). (**B**) Effect on R7 parameter (measure of elastic recovery).

Product/Formulation Challenges

The key challenge for working with niacinamide and nicotinate esters is avoiding hydrolysis to nicotinic acid. Nicotinic acid, even at low doses, can induce an intense skin reddening (flushing) response (30). While a little skin redness (increased skin "pinkness") may be a

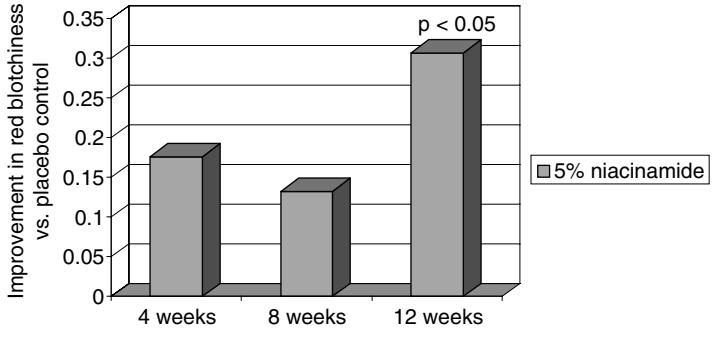

Figure 8 Niacinamide is well tolerated by the skin and even reduces facial skin red blotchiness. Subjects were female Caucasians (n = 50) who applied placebo control versus 5% niacinamide formulations to their faces (12-week, double-blind, split-face, left-right randomized clinical trial).

desired effect, the flushing response among individuals is highly variable in terms of dose to induce it, time to onset of the response, and duration of response. Additionally, the flushing can also have associated issues such as burn, sting, and itch, particularly under cold and/or dry conditions. To avoid hydrolysis, formulating in the pH range of 5 to 7 is preferred. This flushing issue also requires that the purity of the raw material (e.g., niacinamide) be very high to minimize any contaminating free acid.

For the nicotinate esters, there are many commercial options. Many of them unfortunately are readily hydrolyzed to nicotinic acid on or in the skin such that flushing responses occur rapidly (within seconds/minutes) even at very low concentrations ($<1\%$). The longer chain esters (e.g., myristoyl-nicotinate) apparently are more resistant to this hydrolysis and thus appear to be more suitable for use topically.

VITAMIN C

Forms

Of the many forms of this vitamin, some of the more commonly used are ascorbic acid, ascorbyl phosphate (typically as the magnesium and sodium salts), and other ascorbate derivatives (e.g., ascorbyl palmitate, ascorbyl glucoside).

Mechanisms

Vitamin C is well known as an antioxidant and has been utilized as a skin lightener (e.g., via tyrosinase inhibition and/or its antioxidant effect). It also has been reported to have anti-inflammatory properties since it reduces the erythema associated with post-operative laser resurfacing (32). In addition, ascorbic acid also serves as an essential co-factor for the enzymes lysyl hydroxylase and prolyl hydroxylase, both of which are required for post-translational processing in collagen (Types I and III) biosynthesis (33–36). Thus, by stimulating these biosynthetic steps, ascorbic acid will increase the production of collagen which will lead to wrinkle reduction as discussed above.

While the ascorbic acid derivatives may possess some properties of the free acid (e.g., antioxidant), hydrolysis of the derivatives would be required for the increased collagen production effect since the acid is the active co-factor. Demonstration of the hydrolysis of all these derivatives in skin has not been well documented.

Efficacy

There are several published studies discussing the anti-aging benefit of ascorbic acid. The reported doses of vitamin C tested are fairly high, and the base sizes are relatively small ($n \leq 23$). Some of the studies address ingredient oxidative stability, a particular challenge with this form of vitamin C. In oil-in-water emulsion, loss of nearly half of the ascorbic acid in a month is typical (37). To achieve stability, these authors used oxygen impermeable aluminum tube packaging which reduced ascorbic acid loss to less than 10%. After one week of topical treatment of human skin, there was significant reduction of UVA-induced oxidation by 3% ascorbic (41% reduction), whereas the reduction by 3% sodium ascorbyl phosphate was smaller (16%) and not significant. In a double-blind, placebo-controlled, split-face 12-week study (37), stabilized 3% ascorbic acid applied topically ($n = 23$) was found to be well tolerated by the skin and reduced facial wrinkles as determined by skin replica analysis (Fig. 9).

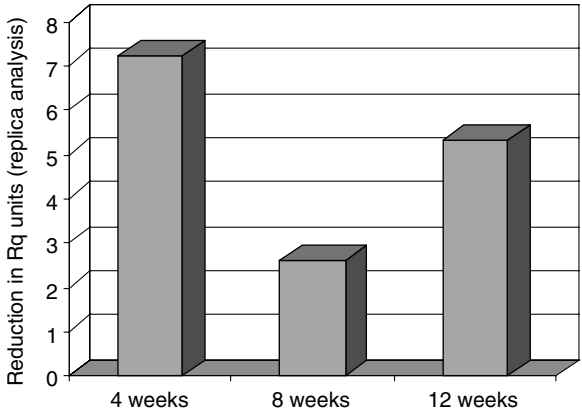

Figure 9 Facial wrinkle reduction (skin replica analysis) by topical 3% ascorbic acid.

In another double-blind, placebo-controlled, split-face 12-week study (38), 17% vitamin C (10% as ascorbic acid and 7% as tetrahexyldecyl ascorbate; n = 10) in an anhydrous gel was applied topically. Based on dermatologist grading, there was reduced facial photoaging. From histological assessment of biopsy specimens, there was improvement in the collagen (increased Grenz zone). In a third study (39), topical 5% ascorbic acid (n = 20, 6 months) improved photodamaged forearm and upper chest skin based on dermatologist scores, skin surface replicas, and biopsy specimen analysis (improvements in elastin and collagen fiber appearance). And lastly, a three-month study (40) of a stabilized ascorbic acid formulation (specific concentration and pH not specified, but likely approximately 10% ascorbic acid at low pH) revealed improvement in facial skin based on dermatologist grading and facial image analysis. However, this formulation led to instances of aesthetic issues for test subjects (sting, erythema, dryness) which may have contributed to the very high drop-out rate in this study (started with n = 28, with n = 19 finishing the study).

Product/Formulation Challenges

The key challenge with vitamin C compounds in general is stability (oxygen sensitivity), particularly with ascorbic acid. Not only does oxidation lead to loss of the active material, there is also rapid product yellowing (an aesthetic negative for the consumer). Various stabilization strategies can be attempted to address the issue, such as exclusion of oxygen during formulation, oxygen impermeable packaging, encapsulation, low pH, minimization of water, and inclusion of other antioxidants. In spite of all those approaches, in general ascorbate stability remains a challenge, and some of these approaches (e.g., very low pH) can lead to unwanted aesthetic skin effects as noted above.

For the ascorbyl phosphates (Mg and Na salts), the resulting high content of salt in product can dramatically impact the thickener system, requiring increased use of thickener ingredients. These ascorbate derivatives are also considerably more expensive than other ascorbate compounds.

Another challenge is skin delivery. Ascorbic acid's penetration across skin is in general poor (typically less than 1% of the topical dose entering skin). For the phosphate derivates of ascorbate, skin penetration can be an even greater challenge due to the

negative charges on the phosphate moiety. Thus, the use of skin penetration enhancement approaches is desired.

PEPTIDES

Forms

There is a limitless array of possible peptides, based on amino acid sequence, number of amino acid residues, and use of derivatives/isomers of these residues. A few peptides with well-characterized sequences that have received particular focus in the cosmetic industry are palmitoyl-lysine-threonine-threonine-lysine-serine (pal-KTTKS; Matrixyl®), acetyl-glutamate-glutamate-methionine-glutamine-arginine-arginine (Ac-EEMQRR; Argireline®), and the tripeptide copper glycine-histidine-lysine (Cu-GHK).

Mechanisms

KTTKS is a fragment of dermal collagen and has been shown to stimulate production of collagen and thus has been discussed in regard to wound healing (41). Incorporation of long-chain lipophilic residues such as palmitoyl onto peptides can dramatically improve their delivery into skin, e.g., the observed five- to six-fold increase in delivery of palmitoyl peptides versus their underivatized versions (42). Thus, pal-KTTKS was synthesized specifically for topical use of this peptide. Like the underivatized peptide, the palmitate derivative (pal-KTTKS) is also active in stimulating collagen production (43–45). In addition, at extremely low levels (ppb) in culture, pal-KTTKS reduces excess dermal GAGs (Fig. 10). As discussed above, this effect may also contribute to an anti-wrinkle effect.

Like KTTKS, GHK is also a fragment of dermal collagen (46). Copper is a required factor for activity of lysyl oxidase, an enzyme involved in collagen synthesis (47). The complex of these two (Cu-GHK) has been shown to stimulate wound healing processes

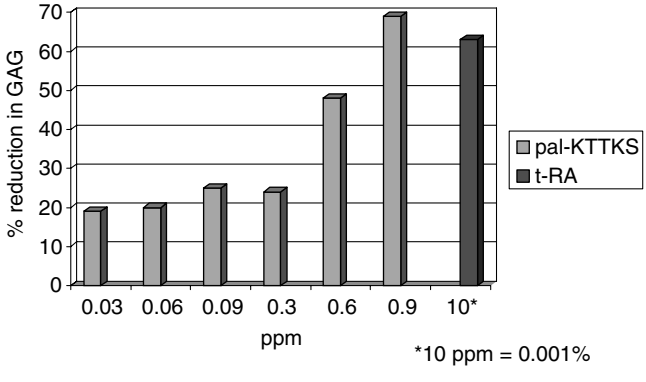

Figure 10 Pal-KTTKS reduces excess dermal GAGs. In cell culture, using fibroblasts from an old donor (57 years old), there was a two- to three-fold increase in GAGs (measured as hyaluronic acid) versus from a young donor (neonatal). Pal-KTTKS was effective in reducing the excess GAG level in old fibroblasts. *Abbreviation*: t-RA, trans-retinoic acid.

in laboratory model systems by increasing production of dermal matrix components such as collagen and specific matrix remodeling matrix metalloproteinases (MMPs) (48–52).

Ac-EEMQRR is described as a mimic of botulinum neurotoxin (Botox®) which functions by inhibiting neurotransmitter release, thus "relaxing" the muscles involved in defining facial wrinkles (53).

Since the reported mechanisms of pal-KTTKS and Cu-GHK involve matrix production and remodeling, their appearance benefits would be expected to require chronic treatment. In contrast, Ac-EEMQRR should have acute benefit effects based on its reported Botox®-like mechanism.

Efficacy

The peptide pal-KTTKS has been shown to be quite potent clinically, providing effects from very low topical doses. This low dose for clinical activity is consistent with the very low concentration (as low as ppb) required to obtain effects in vitro as noted above. In small-base human clinical testing (54), topical pal-KTTKS at 3 ppm was described as providing improvement in appearance of wrinkled skin. To confirm this observation, a larger base size 12-week, double-blind, placebo-controlled, split-face, left-right randomized study (n = 94) was conducted (43), again testing the effect of topical 3 ppm pal-KTTKS. This topical peptide is extremely well tolerated by test subjects, i.e., it does not induce skin irritation responses (no redness, dryness, burn, sting, or itch responses). Based on quantitative computer image analysis, it reduced fine lines/wrinkles versus the placebo control (Fig. 11). While the effect was small, it was significant at weeks 8 and 12. Expert graders evaluating blind-coded images also identified an improvement in fine lines/wrinkles, with directional and significant effects noted at weeks 8 and 12, respectively (Fig. 12). Consistent with the good skin tolerance of the peptide, there was no impact on skin barrier function, as assessed by TEWL (Table 1), indicating lack of irritation.

In contrast to the potency of pal-KTTKS, the reported effects of other peptides require much higher doses, such as 2% for Cu-GHK and as high as 10% for Ac-EEMQRR. There is also limited published information available on the clinical effects of these peptides. One study (55) describes increases in skin thickness, hydration, and smoothness from topical use of a commercial product containing Cu-GHK (peptide dose not indicated) in an open-label study involving 40 subjects. A series of clinical studies of eight to 12 weeks, duration (up to n = 71) describing skin improvements such as reduced

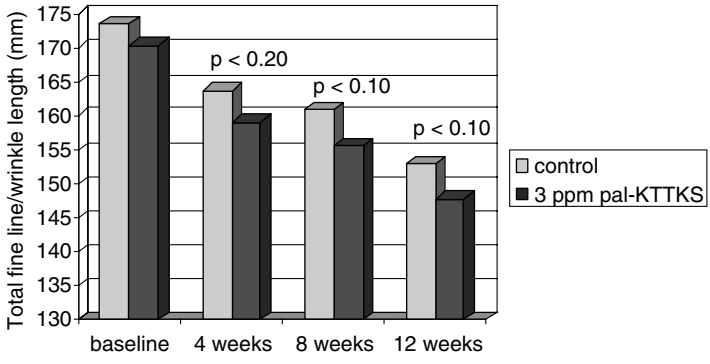

Figure 11 Topical pal-KTTKS improves the appearance of facial skin wrinkles (quantitative computer image analysis). Smaller numbers indicate fewer fine lines/wrinkles.

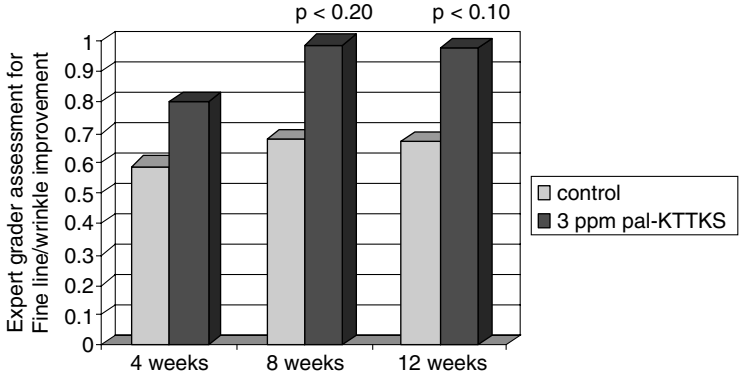

Figure 12 Topical pal-KTTKS improves the appearance of facial skin wrinkles (blinded expert grader image analysis). Grading was on a 0–4 grading scale. Larger numbers indicate fewer fine lines/wrinkles.

wrinkling, apparently using topical 2% Cu-GHK, have been presented as meeting posters (56–59). For Ac-EEMQRR, a conference platform presentation (53) describes 30% reduction in wrinkle depth with 10% of this peptide used topically in a 30-day study.

Product/Formulation Challenges

An important challenge is delivery into skin since peptides are poorly penetrating, especially as the number of amino acid residues increases. An approach to that problem is addition of a lipophilic chain (e.g., palmitate), which in the case of KTTKS increased skin penetration several-fold over the underivatized peptide.

An additional challenge is the cost. As the number of amino acid residues increases, the cost of peptide can increase dramatically. The consequences are that only low levels of peptide can be used in product (which is acceptable if the peptide is potent as in the case of pal-KTTKS) or the finished product cost to the consumer must be very high.

DIMETHYLAMINOETHANOL (DMAE)

Mechanism

DMAE (also known as deanol) is a precursor to acetylcholine, a neurotransmitter involved in increased muscle tone. There thus could be firming of the skin via effects on the facial

Table 1 Lack of Effect of Pal-KTTKS on Skin Barrier Properties as Assessed by Transepidermal Water Loss

	Transepidermal water loss (g water/m^2/hr)		
Time point	Placebo formulation	Pal-KTTKS formulation	p value
Baseline	11.15	11.40	$p > 0.38$
4 weeks	8.10	8.24	$p > 0.60$
8 weeks	8.56	8.41	$p > 0.60$
12 weeks	7.89	8.15	$p > 0.35$

musculature. In addition, acetylcholine may affect the keratinocytes (specifically their proliferation, adhesion, and motility) leading to "epidermal contractility," leading to a firming/tightening effect on the skin (60). DMAE also has antioxidant properties, which may contribute to its anti-aging effects (61,62).

Efficacy

Several studies have been discussed and overviewed (60). For example, in an open-label, one-month study with a DMAE-containing formulation (DMAE dose not specified), the skin of 50 subjects was compared at the end of the treatment period versus baseline by dermatologist grading and subject self-assessment. Significant improvements were reported in several measures, particularly in the area of skin firming and lifting. The topical treatment was well tolerated by the subjects. As a further example, in a double-blind, placebo-controlled, 16-week, full-face study (n = 156), 75% of the subjects used a DMAE-containing formulation (DMAE dose not specified), and 25% of the subjects used a placebo formulation (60). Effects were determined based on dermatologist grading and image analysis. The statistical p value presentation indicates several facial benefits related to skin firming (e.g., under-eye firming, cheek area firming, jaw line lifting and firming, increased elasticity, etc.). Again, the skin tolerated the DMAE formulation well. These reported observations are consistent with other small-base (n = 8) clinical testing showing improved skin firmness instrumentally from topical use of 3% DMAE in a one-day study (63).

The interesting aspect of the clinical effects is that while some testing has been weeks/months in duration, the onset of the benefit was reported to be very rapid, within minutes of topical application (60,63). This seems consistent with the suggested mechanism if sufficient DMAE can penetrate into skin and be converted to acetylcholine in such a short time period.

Product/Formulation Challenge

DMAE, a base, has historically been used as a formula pH adjusting agent. In the un-neutralized state, its pH is approximately 10. Thus, pH adjustment to the desired value appears to be sufficient.

KINETIN (N_6-FURFURYLADENINE)

Mechanisms

Kinetin is a plant hormone. While its specific mechanisms have not been elucidated, it has been observed to promote growth and have anti-senescence effects in plants. It is a powerful natural antioxidant with effects in protecting DNA and protein from oxidative damage. In human fibroblast cell culture, even very low levels (ppm) delay the onset of changes associated with cell aging, e.g., appearance of lipofuscin, appearance of multinucleate cells, and microtubule disorganization (64).

Efficacy

In three reported clinical tests (10–24-week duration, n = 30–98), topical 0.1% kinetin was reported to improve several aging skin problems, such as wrinkling, poor texture, and hyperpigmentation (64). All of these studies apparently did not involve a placebo control,

but rather were comparisons (dermatologist grading and self-assessment) of treatment effects versus baseline. The 0.1% dose is well tolerated by the skin, with no significant irritation issues described.

Product/Formulation Challenge

The limitation with kinetin is its fairly low solubility in formulation. This restricts the upper dose to approximately 0.1% for an aesthetically elegant formulation. This also impacts delivery into skin, although even from this relatively low dose sufficient material does enter skin to provide clinical effects.

TRITERPENOIDS

Forms

There are numerous plant-derived triterpenoid compounds and derivatives of them, with a few receiving attention in the cosmetic area, e.g., asiatic acid, ursolic acid, medacassic acid, oleanolic acid, betulinic acid, and boswellic acid. There are also naturally occurring saccharide esters of these, such as asiaticoside, which is the ester of asiatic acid.

Mechanisms

There are many reported mechanisms for triterpenoids, for example, antioxidant, anti-inflammatory, elastase inhibition, wound healing, and promotion of collagen and ceramide production (65,66). Since triterpenoids share some structural similarity to steroidal compounds such as hydrocortisone, they may also share some of the mechanistic properties and potency of such compounds (e.g., anti-inflammatory effects).

Efficacy

There is little published information to illustrate the clinical effects of triterpenoids. Topical ursolic acid in liposomes (final concentration of ursolic acid $<0.002\%$) resulted in increased skin ceramides in small-base forearm testing ($n=3$; 11 days of treatment). The increased ceramides were suggested to indicate improved skin barrier (66). In a double-blind, placebo-controlled, left-right randomized forearm clinical study of 20 subjects (67), treatment with topical liposomal triterpenoid (specific content not indicated) was done for one month. Improvements in skin extensibility and firmness (instrumentally determined) were reported. While the dose of triterpenoid was not specified, it was probably low and apparently consisted of a blend of boswellic acid, asiatic acid, and possibly others since the content may have included extracts.

Product/Formulation Challenge

The key issue with triterpenoids is poor solubility which also results in limited skin delivery. Formulation in liposomes has been employed to improve both delivery and formula solubility, although the resulting increase in oil content of the formulations may negatively impact the aesthetics.

UBIQUINONE (CO-ENZYME Q10)

Mechanism

Ubiquinone is an endogenous antioxidant present throughout the body, including the skin. The levels decrease with age. Topical ubiquinone replenishes the skin (68).

Efficacy

While much has been discussed regarding the skin care benefits of topical ubiquinone, the available data address only the antioxidant properties of this ingredient (69).

Product/Formulation Challenge

Ubiquinone is yellow-orange in color. Thus, only low doses ($<1\%$) can be used in topical cosmetic skin care products to avoid aesthetic color concerns. This low dose likely limits the benefit potential of this ingredient.

OTHER TECHNOLOGIES

Hydroxy and Keto Acids

There are many compounds within this group: alpha-hydroxy acids such as glycolic acid and lactic acid, alpha-keto acids such as pyruvic acid, and beta-hydroxy acids such as salicylic acid. Their mechanism involves accelerated exfoliation of stratum corneum, leading to a variety of skin surface texture and color appearance improvement effects. These materials are the subject of another chapter in this volume.

Moisturizers

Topical materials such as glycerol and hyaluronic acid will readily hydrate the skin surface and will diminish the appearance of fine lines simply by plumping the skin. Moisturizers are the subject of another chapter in this volume.

Flavonoids

This family of plant-derived and synthetically prepared chemicals encompasses a huge variety of compounds. They are beginning to appear in cosmetic products and are a fertile area for identification of materials active in improving aging skin.

Plant Extract Components

In addition to flavonoids, plant extracts are a rich source of diverse compounds that are being explored to identify skin care bioactives.

DISCUSSION

It is clear that many anti-aging ingredients that are used cosmetically do provide appearance improvement benefits to the skin, but for others data supporting their claimed effects are not readily available for assessment. For the active ones, while the benefits

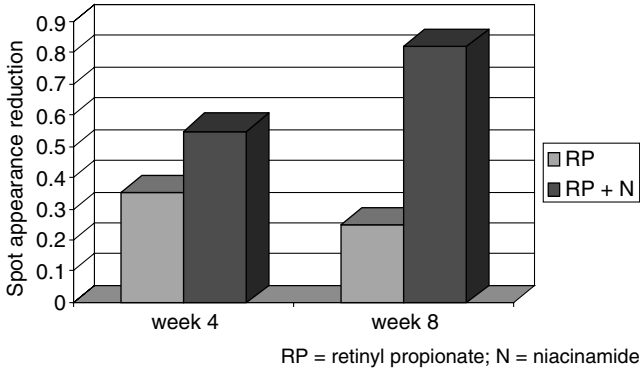

Figure 13 Combining niacinamide with retinyl propionate increases the skin appearance improvement effect.

may be small, they are significant and do meaningfully improve skin appearance with continued use of the materials. It is difficult to quantitatively compare the magnitude of the effects among the various technologies since there are many variables across studies: the specific end points measured are often different (e.g., surface replicas vs. facial image analysis), equipment and method sensitivities vary, formulation types vary which can impact active delivery into skin, different body sites were used (e.g., forearm vs. face), clinical base sizes ranged from very small to large, etc. But it is reasonable to state that they are all less effective than a technology such as trans-RA. This simply presents an opportunity to identify more potent cosmetic materials.

While the benefits of current technology may be small, the magnitude can increase by combining materials, especially those with different mechanisms of action. For example, combining a vitamin B3 with a vitamin A (Fig. 13) or with a peptide (Fig. 14) leads to greater benefits than the individual materials. There is certainly opportunity to continue to explore this avenue.

There is ample room for exploration of new materials within the current classes of compounds (e.g., peptides) and in newer classes of compounds (e.g., flavonoids).

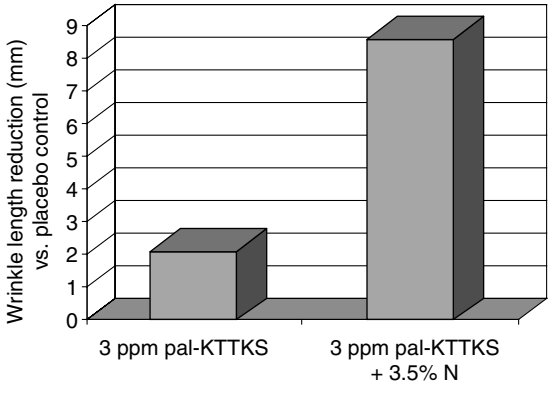

Figure 14 Combining niacinamide (N) with pal-KTTKS increases the skin appearance improvement effect.

Considering the enormous diversity of compounds to be found in natural extracts, for example, the future possibilities seem limitless for identifying new active materials and mechanisms to improve the appearance of aging skin.

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12
The Role of Cosmeceuticals in Dermatology

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WHAT ARE "COSMECEUTICALS"—COSMETICS VS. RX DRUGS

History and Background

The term "cosmeceuticals" was first popularized about twenty-five years ago by Albert Kligman, MD, PhD, to bridge the gap between cosmetics and drugs or pharmaceuticals. Historically, after the Food, Drug, and Cosmetic Act of 1938, the world of topical skin care products was divided into two groups: cosmetics and drugs. Drugs were for the treatment or prevention of diseases, and it was required that safety and efficacy be established before sales and marketing could proceed. In contrast, cosmetics were viewed as agents to enhance the beauty of the skin or improve the appearance of the skin, and safety and efficacy were not required to be demonstrated before sales and marketing of these products (1).

Another organization, the Cosmetic, Toiletry, and Fragrance Association (CFTA), in the United States was formed in 1894 and today serves as a valuable liaison among suppliers, manufacturers, and distributors of cosmetic products for the personal care industry. No formal organization exists at this time specifically for the cosmeceutical realm.

At a fundamental level cosmetics are products which affect the appearance of the skin, while drugs affect the structure and function of the skin. Thus the term "cosmeceutical" is intended to describe skin care products that fall in between these categories. Increasingly though products which are considered cosmeceuticals actually do affect the structure or function of the skin and thus have drug-like effects but are marketed using appearance-based claims. This has given rise to much confusion and ironically may provide some disincentive for manufacturers to conduct or publicize clinical testing since the data generated may support the drug-like effects. For example, a drug may be marketed as a product that "reduces wrinkles by stimulating collagen production," but a cosmetic which could potentially have essentially the same mechanism of action and clinical effects would be marketed as a product that "reduces the appearance of wrinkles." While some

cosmeceuticals are "drugs in disguise" as cosmetics, if marketing claims push the edge of the claims envelope too hard, then the Food and Drug Administration (FDA) may intervene with various warnings or actions; thus, the issue of "when" does a cosmeceutical become a drug is likely to become more significant in the future (2,3).

If one looks at sunscreens and antiperspirants, these are regulated as over-the-counter (OTC) drugs in the United States but not in Europe. One need only look at the delays in availability in the United States of some of the new and highly effective sunscreens to appreciate some of the archaic aspects of the 1938 legislation. Thus the term "cosmeceutical" encompasses a broad range of the ill-defined territory which lies between cosmetics and drugs. It is a very useful concept scientifically and has been accordingly embraced on a broad global scale. The years ahead will see a struggle to define and refine this cosmeceutical concept. Some exemplary efforts towards this have been made in Japan, but a global uniform concept is yet to emerge (4).

The Skin's Response to Environmental Damage and Chronologic Aging

The skin is the body's first line of defense for environmental exposure. Much of the "premature" aging (in contrast to intrinsic or chronologic aging) occurs as a direct or indirect result of the skin's interaction with its environment. While photoaging is properly recognized as one of the principal causes of aging in lighter skin types, many other factors are also significant. For example, tobacco smoke produces a host of problems and in some darker skinned ethnic populations may be the primary cause of wrinkles rather than ultraviolet (UV) light. Ozone, air pollution, industrial, occupational, or recreational exposures bring contact with a diverse array of potential toxins. Personal skin care habits and excessive or improper use of products can also cause problems. Disease and drugs and therapies for diseases may produce many challenges to the skin as well.

Traditionally the sun protection factor (SPF) has been the primary focus of protection from the environment for UV light. Various moisturizer products have some function for barrier protection (5–7). However, there is a growing realization that the issues are more complex than this. As a result, discussion is growing about SPF to include a broader range of UV exposure including UVA-1 wavelengths. You will be reading more about immune protection factor (IPF) and also environmental protection factor (EPF) in the years ahead as our understanding of the full spectrum of environmental insults to the skin is explored.

The common pathways of much of the environmental damage to the skin are twofold: free radical generation and DNA damage. The concept of repetitive small "injuries" to the skin resulting in cumulative long term chronic alteration of the optimal structure and function of the skin resulting in "scars" is a good one. In this scenario wrinkles might be considered "solar scars" … or "tobacco scars" … or "environmental injury scars." The latter is more comprehensive, but the former are useful teaching tools for educating our patients. The growing evidence that environmental damage reduces the efficiency of mitochondrial ATP production provides a unique area of future research. The ability to "re-energize" skin cells as one ages using cosmeceuticals is another very exciting area for the future (8,9).

If one considers environmental damage then the first goal of therapy is avoidance … followed by protection … then minimizing or neutralizing free radical damage … and finally repair or restorative treatments. As clinicians we try to focus on all of these factors and develop practical, useful, and affordable treatment plans that adapt to our patient's

lifestyle so that compliance is maximized. One of the great challenges with the proliferation of cosmeceuticals is finding good scientific and clinical data like we are accustomed to having for our pharmaceutical drug therapies. Such information is often absent or studies are poorly designed and physicians are often left sorting through marketing claims instead of scientific data.

This scenario has led to the increasingly popular practice of dispensing cosmeceuticals within the physician's office. This provides the physician with the ability to control and select products that are scientifically based, but it also opens the door for misuse of the privilege and trust that our patients place in us. The American Academy of Dermatology has a formal policy and guidelines for this practice which is useful to review (Fig. 1) (10).

Properly used, office dispensing can be a very valuable tool for the optimal use of cosmeceuticals (11). Dispensing "private label" products to "control" patient purchase habits or using products which have no scientific or clinical basis established is a good example of practices which do not enhance the physician's professional stature nor benefit the consumer. Since nearly half of dermatologists currently dispense products, the need for better educational resources for physicians is growing and the availability of textbooks such as this are one part of the effort to put cosmeceutical skin care on a solid scientific and academic basis.

The sales growth of cosmeceuticals is dramatically increasing relative to skin care products in general with special interest for the anti-aging category of products. This trend is likely to continue. The consumers have a need for reliable information, not just marketing claims. Physicians are the traditional source of such information; however, many are poorly informed and their patients are increasingly seeking this expertise and advice elsewhere at non-traditional and often non-medical sources. With the proliferation of products and marketing claims that are ahead of or unsupported by clinical data, it is truly an information wilderness for many products.

RX vs. Cosmetics—the Response of the Skin's Structure and Function to Cosmeceuticals

The skin plays many roles ranging from barrier function to highly complex biochemical and photobiochemical processes. If we follow the definition above then cosmeceuticals are inherently not simply cosmetics to beautify the appearance of the skin.

American Academy of Dermatology Office Dispensing Guidelines for Prescription and Non-prescription Products
* DO NOT place your own financial interests above the well-being of patients
* DO NOT price products at an excessive mark-up
* DO NOT create an atmosphere of coercive selling
* DO NOT sell products whose claims of benefit lack validity
* DO NOT represent products as "special formulations" not available elsewhere if this is not the case
* DO clearly list all ingredients, including generic names of drugs
* DO advise patients of alternative purchase options if products are available elsewhere
* DO provide prescription refills that can be filled outside the office if patients so choose

Figure 1 American Academy of Dermatology Office Dispensing Guidelines for Prescription and Non-prescription Products. *Source*: American Academy of Dermatology, 2003.

Cosmeceuticals then affect either the structure or the function (or both) of the skin. Unlike drugs, cosmeceuticals typically are very safe and have few significant serious adverse events. However, like drugs, these active agents can impact many diverse functions of the skin and we do not fully comprehend the implications of these actions in many cases.

For example, take botanical-based actives in cosmeceuticals. These plant-derived substances have the potential for contact dermatitis like reactions similar to poison ivy dermatitis. Irritant reactions are also possible as are phytophotodermatoses. Typically products are selected which do not pose these concerns and also the concentrations used in the formulations are below the threshold of reaction (12).

There are also issues of bioequivalency. Most physicians recall the use of digitalis in past for cardiac treatments—before standardized digoxin became available. An example with cosmeceuticals is that the polyphenol content of a particular botanical may vary from brand to brand; even though the percentage concentration of that active seems equal among brands, the difference in polyphenol content may make one product less efficacious than the other brand, which has a higher content of polyphenols (13).

Another example of an issue is with one of the very popular alpha-hydroxy acid (AHA) actives, glycolic acid, where the pH and pKa values impact the clinical effects and side effects. For these products, simply comparing the percentage of glycolic acid did not provide the physician, esthetician, or consumer with an accurate assessment of the effects on the skin. In fact, a lower percent glycolic acid product could potentially be more irritating than a higher percentage glycolic acid product depending on the pH (14,15).

An issue infrequently discussed is that of pesticide residues or other contaminants for botanicals. So bioequivalency and bioavailability and purity are all issues for these types of active ingredients. Also, while we are thinking in the "drug" pattern, the "dose" is important. So the percentage of actual active ingredient also determines to some extent the effects of cosmeceuticals compared to Rx drugs. Also, physician-dispensed products often have a higher "dose" or concentration of actives than the OTC products.

Other factors are synergistic reactions and stability. Many cosmeceutical formulations have complex mixtures of actives the interactions of which are not all well defined. Some antioxidants are not that stable and others may be unstable after they are opened. Novel new "airless" pump delivery systems or mixing as pumped onto skin from applicator provide ways to combat these problems.

Data on the relative potency is often lacking on active ingredients within the same category. Antioxidants are a good example, and this data has only recently begun to be published. Much of the data about the drug-like effects on the skin's structure and function are considered proprietary and not available for physicians or the consumer to review. Additionally many products are sold widely with minimal scientific or clinical data whatsoever. Thus, while cosmeceuticals increasingly affect the skin's structure and function like drugs, the data that is traditionally available for drug evaluation is often incomplete or nonexistent. The great safety of most cosmeceutical actives is one of the mitigating factors in this scenario. We will see antioxidants grow dramatically in their role with the cosmeceutical armamentarium to protect and also in some cases repair environmental damage and aging in general.

In summary, cosmeceuticals may have profound effects on the structure and/or function of the skin—or they may have little or no effect and behave like cosmetics. A comprehensive discussion of this is beyond the scope of this section, but the use of cosmeceuticals to improve the appearance and health of the skin is a fascinating area of science and one which we will see explored and mapped in the years ahead.

DOMESTIC AND INTERNATIONAL REGULATORY GUIDELINES IMPACTING COSMETICS

Domestic Regulations

There have been many misunderstandings relating to the regulation of cosmetic products and OTC drugs in the United States. For the most part, the cosmetic industry has never been directly regulated by any government agency and does not require the FDA to approve a cosmetic/cosmeceutical product prior to marketing. Additionally, in 1972 the FDA initiated a monograph process for OTC drugs which eliminated the need to have pre-market approval for certain product categories (sunscreens, antiperspirants, anti-acne, etc.) by companies prior to being sold to consumers. The process of regulation for cosmetics and OTC drugs would appear to be better described as "self-regulated" and, therefore, impacted by various guidelines, legislation, and regulatory bodies as opposed to governed by these entities. Outlined below is a brief review of the laws that are currently in place. A more detailed review can be obtained through other references and/or review of the various regulatory agency Web sites (FDA.gov, FTC.gov, EPA.gov, etc.) (16).

The most important regulations to note are the Food, Drug, and Cosmetic Act of 1938 and the 1960 amendment, the Fair Packaging and Trade Act of 1966 and 1973, the OTC Drug Monograph Process introduced in 1972, and the 1916 Federal Trade Commission Act. With the exception of the latter, which is governed by the FTC, the others are the responsibility of the FDA. Additionally, there have been laws brought about by individual members of the government (Delaney Amendment in 1958—anti-cancer act) as well as by individual state legislatures (California, New York, New Jersey, and Massachusetts, to name a few) which relate to areas such as the Volatile Organic Compounds (VOCs) and the Safe Drinking Water and Toxic Enforcement Act (Proposition 65). Lastly, it should be noted that cosmetic manufacturers are allowed to use any ingredient in a product, as long as the product has been tested and shown to be safe for its intended use, with the exception of hexachlorophene, mercury compounds, chlorofluorocarbon propellants, bithionol, halogenated salicylanilides, chloroform, vinyl chloride (aerosol products), zirconium (aerosol products), methylene chloride, acetylethyltetramethyltetralin, musk ambrette, 6-methylcoumarin, nitrosamines, dioxane, and estrogen.

International Regulations

Numerous countries all around the world have recently instituted some form of cosmetic regulation, other than product registration with their ministries of health, with respect to protecting the consumers of their respective countries. The amount of information is massive and to simply list current activities would go far beyond the scope of this chapter. However, it should be noted that Australia (http://www.nicnas.gov.au/) as well as Canada (http://www.hc-sc.gc.ca/english/media/releases/2004/cosmetic_labelling.htm) have taken very proactive approaches to cosmetic regulation, and the Web sites noted above can be accessed for additional information if so desired. The European Union (EU) has probably been the most proactive globally in attempting to regulate cosmetics. New provisions made in the seventh amendment to the EU cosmetic directives are outlined below identifying some of the significant changes in how cosmetic manufacturers will need to do business in the EU as well as what information will need to be provided to consumers in order for the product to be sold in the various EU countries. These regulations are all in effect as of March 11, 2005.

- A product information dossier on qualitative and quantitative composition of the product and existing data on undesirable effects must be made "easily accessible to the public by means including electronic means." Companies can list themselves and this information in the European Cosmetic Toiletry and Perfumery Association (COLIPA) database (www.European-Cosmetics.info). Additionally, the dossier must include information on any animal testing relating to development or safety evaluation of a product or ingredient.
- A Quantitative Declaration of Ingredients containing any ingredient(s) listed in the Dangerous Substances Directive (67/548/EEC) must list the concentration or concentration range of the substance(s) in question.
- Information on Undesirable Effects on Human Health Resulting from Use of the Cosmetic Product. Undesirable effects are, essentially, irritant or allergic reactions that can in rare cases affect skin or eyes. It is also recommended that companies present the number of undesirable effects in context of the number of units placed in the marketplace (i.e., to date there have been zero undesirable effects per one million units placed in the EU market).
- A ban on animal testing went into effect immediately for finished products and for ingredients.
- Need exclusive exposure assessments for products intended for children under 3 years of age and for intimate hygiene products.
- Color additives for the entire range of decorative cosmetics may be listed at the end of the ingredient list after the term "may contain" or the symbol "+/−."
- Any ingredient identified as carcinogenic, mutagenic, and/or a reproductive hazard (CMR) Category 1 and 2 must not be intentionally added to cosmetic products. Any ingredient identified as CMR Category 3 must not be intentionally added unless evaluated by SCCNFP and found acceptable for use in cosmetic products.
- Products that have a durability (shelf life) over thirty months must have the a "Period After Opening" (PAO) symbolized by an open jar with the number of months which indicates how long after a product is opened it can be used without harm to the consumer (see example below under "How to Select the 'Best' Formulation of a Cosmeceutical."
- Problem fragrance ingredients (26 fragrances ingredients with a history for contact dermatitis) need to be labeled by INCI name in the ingredient label if they are used in the formula at 0.001% in leave-on and 0.01% in rinse-off products.

CATEGORIES OF CURRENTLY POPULAR COSMECEUTICALS IN DERMATOLOGY

Amino Filaggrin Acids—Filaggrin Protein/Fruit Acids

1. *Science and clinical studies*: Although no peer review articles were found, studies outlined by the manufacturer of the product claim that the product has been tested over the last three years and is effective in reducing the appearance of visible lines and improving tone and texture of the skin.
2. *Key benefits*: Amino Filaggrin Acids (AFAs) are amino acids that are naturally found in skin and are associated with increasing moisture retention in skin. They claim to be able to penetrate through the keratinized epidermis.

3. *Primary adverse effects*: None found. Considered to be milder than AHA or BHA preparations.
4. *Practical applications in dermatology*: AFA in-office peels may be used on an alternating basis with AHA peels, or may be helpful in patients having problems with long term use of various peeling agents. Can be used with microdermabrasion or other minimally invasive procedures.

Vitamins: C and E

1. *Science and clinical studies*: Numerous studies have been published on both of these ingredients relating to antioxidant function and protection against UV damage. Additionally, vitamin C has been shown to enhance collagen and elastin production. Both ingredients are essential in a formula if any antioxidant and/or anti-aging claims are to be made. The two ingredients work together to a redox manner to neutralize free radicals by converting to both a pro-oxidative and natural state.
2. *Key benefits*: Vitamin E is an effective antioxidant which can act synergistically with vitamin C to help fight against free radical damage associated with premature aging.
3. *Primary adverse effects*: Although uncommon, some contact dermatitis reactions have been reported to vitamin E over the years as well as irritant reactions caused by vitamin C due to some products low pH.
4. *Practical applications in dermatology*: Used alone or in combination these antioxidants have a variety of applications for anti-aging.

Vitamins: K

1. *Science and clinical studies*: Two studies have been published whereby vitamin K has been used to minimize purpura production after pulse dye laser treatments (17). Both studies employed approximately 20 subjects, with one evaluating the effects of the ingredient alone and the other with the use of retinol BID weeks before and two weeks after laser treatment. The side of the face treated with topical vitamin K with or without retinol demonstrated significantly lower scores of bruising severity when compared with the side treated with placebo (18).
2. *Key benefits*: Reduces bruising and can minimize damage associated with pulse dye lasers.
3. *Primary adverse effects*: None noted.
4. *Practical applications in dermatology*: Using vitamin K, two weeks before and after pulse dye laser treatments may reduce adverse cutaneous reactions. Efficacy for bruising from other etiologies is unknown.

Vitamins: B3 (Niacinamide)

1. *Science and clinical studies*: Niacinamide was evaluated clinically in Japanese women for the inhibition of pigmentation. Eighteen subjects with hyperpigmentation received either a 5% Niacinamide containing product or a placebo. Additionally, 120 subjects with facial tanning were given either a 2%

Niacinamide cream containing a sunscreen, a sunscreen, or a vehicle. Changes in facial pigmentation were evaluated via computer analysis and visual grading of high-resolution digital images of the face. Niacinamide significantly decreased hyperpigmentation and increased skin lightness compared to vehicle alone after four weeks of use. Other studies have been reported whereby topical Niacinamide application demonstrates improvement of barrier function via decreased transepidermal water loss (TEWL) and skin appeared to be more resistant to irritation produced by topical irritants such as detergents (19,20).

2. *Key benefits*: Decreases hyperpigmentation and may improve barrier function and resiliency to environmental insults.
3. *Primary adverse effects*: Well tolerated.
4. *Practical applications in dermatology*: Niacinamide may be a suitable replacement for treating hyperpigmentation when results are not obtainable with hydroquinone and/or other conventional forms of treatment.

Vitamins: B5 (Panthenol)

1. *Science and clinical studies*: Topical application of Pantothenic Acid has been shown to provide moisturizer-like benefits, improving stratum corneum hydration, reducing transepidermal water loss, and maintaining skin softness and elasticity. Activation of fibroblast proliferation, which is of relevance in wound healing, has been observed both in vitro and in vivo, and accelerated re-epithelization in wound healing has been demonstrated via transepidermal water loss. Pantothenic Acid has also been shown to have an anti-inflammatory effect reducing UV-induced erythema. In double-blind, placebo-controlled clinical trials, a Pantothenic Acid-containing cream resulted in significantly less damage to the stratum corneum barrier, compared with no pretreatment over three to four weeks.
2. *Key benefits*: Moisturizer-like benefits, reduction in TEWL, fibroblast activation, and anti-inflammatory potential.
3. *Primary adverse effects*: Topical administration of Pantothenic Acid preparations are generally well tolerated, with minimal risk of skin irritancy or sensitization.
4. *Practical applications in dermatology*: Pantothenic Acid may be beneficial in patients who have undergone skin transplantation or scar treatment, or therapy for burn injuries and different dermatoses.

Enzymes: SOD

1. *Science and clinical studies*: Superoxide Dismutase (SOD) is the most effective internal antioxidant found in humans. Superoxide radials are reduced to hydrogen peroxides by SOD and then further reduced by catalase to water. Data from the literature indicate a protective effect of SOD in topical application against UV-induced cutaneous damage (21). When an SOD cream containing 0.6 mg/ml of bovine SOD was applied locally onto the skin and mucosal lesions caused by progressive systemic sclerosis, systemic lupus erythematosus, Behcet's disease, herpes simplex, and burns, the lesions and symptoms were rapidly improved in many cases after its administration, even when the

symptoms were stabilized for several weeks before the treatment (22). SOD was concluded to be effective for these conditions. In another study, topical application of free Mn-SOD or Cu, Zn-SOD showed complete healing in a burn patient who was advised to undergo skin transplantation (23). However, the later study noted that SOD dissolved in a white petrolatum vehicle rapidly lost its activity (within three months) and commented that SOD should be dissolved in the vehicle before use (24–26).

2. *Key benefits*: Suppression of UV-induced cutaneous damage and possible reversal of free radical-mediated disease states.
3. *Primary adverse effects*: None known.
4. *Practical applications in dermatology*: May be effective in treating progressive systemic sclerosis, systemic lupus erythematosus, Behcet's disease, herpes simplex, and burns.

Growth Factors: EGF/TGF

1. *Science and clinical studies*: No peer review clinical data was found on the effects associated with epidermal growth factor (EGF/TGF). However, several in vitro studies are obtainable. A bioassay for EGF reported by Carpenter and Zendegui was described as rapid, specific, and extremely sensitive (27). The bioassay detects as little as 25 pg of EGF and was considered more sensitive than commonly used radioreceptor assays and nearly as sensitive as radioimmuno assays. The bioassay involved measurement of the proliferation of cultures of an EGF-requiring cell line and can be carried out in a quantitative manner over a 40-fold range of EGF concentrations. One in vivo study in rabbits evaluated wound healing with a placebo ointment and one containing EGF (28). Less wound contracture occurred in the EGF-treated wounds, and wound maturation occurred earlier. The healed wounds that had been treated with EGF more closely resembled the surrounding normal tissue, producing less local deformity than in the controls. A study evaluating the epidemiological and experimental evidence that dietary polyphenolic plant-derived compounds have anticancer activity is also note worthy (29). The investigators found that green tea components induce apoptosis via a TGF-beta superfamily protein, non-steroidal anti-inflammatory drug activated gene (NAG-1) and showed that ECG is the strongest NAG-1 inducer among the tested catechins and that treatment of HCT-116 cells results in an increasing G(1) sub-population, and cleavage of poly (ADP-ribose) polymerase (PARP), consistent with apoptosis. The data generated by this study elucidate mechanisms of action for components in green tea and was hopeful in leading to the design of more effective anticancer agents and informed clinical trials (30).
2. *Key benefits*: May facilitate wound healing.
3. *Primary adverse effects*: None reported.
4. *Practical applications in dermatology*: May accelerate normal wound healing in patients under going evasive cosmetic procedures.

Growth Factors: Kinetin (Plant Growth Factor)

1. *Science and clinical studies*: Kinetin is a plant-derived nucleotide (growth factor) known to delay senescence (aging) in plants. Two one-year long clinical

studies have been completed on Kinetin. Study results report that Kinetin can reverse the signs of photodamaged skin and improve the overall appearance of the skin, making it smoother and more even in color and visibly diminishing the appearance of fine lines and wrinkles. These studies also demonstrated that Kinetin can significantly improve the skin barrier function and help the skin to retain more moisture, making the skin softer and smoother. Additionally, Kinetin is also thought to process some antioxidant capabilities; however, this activity is not considered to be the mechanism of action for the reversal of photoaging observed in the clinical studies noted.
2. *Key benefits*: It demonstrates antioxidant and barrier function benefits.
3. *Primary adverse effects*: None reported.
4. *Practical applications in dermatology*: May be useful in treating photodamaged skin.

Antioxidants: Alpha-Lipoic Acid

1. *Science and clinical studies*: Topical application of 3% Alpha-Lipoic Acid has been shown to decrease UVB-induced erythema. These observations are thought to reflect the ingredient's ability to function as an antioxidant blocking the transcription factor of nuclear factor-kappa B (NF-kappa B) (31). Clinical testing in 33 women with photodamage indicated that 12 weeks of treatment with a cream containing 5% Lipoic Acid improved clinical characteristics related to photoaging of facial skin (32).
2. *Key benefits*: Antioxidant functions, inhibition of NF-kappa B and secondary oxidative products.
3. *Primary adverse effects*: None known.
4. *Practical applications in dermatology*: May be useful in treating photodamaged skin.

Antioxidants: Co-Q10 (Ubiquinone)

1. *Science and clinical studies*: Co-Q10 plays a vital role in mitochondrial enzymes of the oxidative phosphorylation pathway and is essential for the production of the high-energy phosphate, adenosine triphosphate (ATP), upon which all cellular functions depend. Numerous in vitro studies have been reported demonstrating the antioxidant efficacy of Co-Q10. However, limited clinical studies are available reporting on the benefits of topical administration. One study was found which noted that Co-Q10 penetrates into the viable layers of the epidermis and reduces the level of oxidation measured by weak photon emission and a reduction in wrinkle depth was also shown (33). Co-Q10 also protected against UVA-mediated oxidative stress in human keratinocytes in terms of thiol depletion, activation of specific phosphotyrosine kinases, and prevention of oxidative DNA damage.
2. *Key benefits*: Antioxidant functions which mediate UVA oxidative stress in human keratinocytes minimizing DNA damage.
3. *Primary adverse effects*: None known.
4. *Practical applications in dermatology*: May be useful in treating photodamaged skin.

Antioxidants: Idebenone (Hydroxydecyl Ubiquinone)

1. *Science and clinical studies*: Idebenone is a synthetic version of Co-Q10 with a molecular weight approximately 60% smaller. A multi-step in vitro process utilizing a variety of biochemical and cell-biological methods combined with in vivo studies was designed to compare the oxidative stress protective capacity of commonly used antioxidants. Summarizing and totaling the data equally weighted for each oxidative stress study, the overall oxidative protection capacity score of 95, 80, 68, 55, 52, and 41 was obtained for idebenone, DL-a-tocopherol, kinetin, ubiquinone, L-ascorbic acid, and DL-a-lipoic acid, respectively. The higher the score the better the overall oxidative stress protection capacity of the antioxidant. This multi-step protocol was thought to serve as a standard when investigating and comparing new putative antioxidants for topical use (34). In a non-vehicle control study, 0.5%, and 1.0% idebenone commercial formulations were evaluated in a clinical trial. Forty-one female subjects, age 30–65, with moderate photodamaged skin completed the study. After six weeks of BID use, the 1.0% idebenone formula produced a 26% reduction in skin roughness/dryness, a 37% increase in skin hydration, a 29% reduction in fine lines/wrinkles, and a 33% improvement in overall global assessment of photodamaged skin. The 0.5% idebenone formulation demonstrated a 23% reduction in skin roughness/dryness, a 37% increase in skin hydration, a 27% reduction in fine lines/wrinkles, and a 30% improvement in overall global assessment of photodamaged skin. Additionally, punch biopsies were taken from random select subjects, baseline at and after six weeks, and stained for certain antibodies Interleukin [(IL)-6, IL-1b, Matrixmetalloproteinase (MMP)-1, Collagen I] using immunofluorescence microscopy. The immunofluorescence staining revealed a decrease in IL-1b, IL-6, and MMP-1 and an increase in Collagen I for both concentrations (35).
2. *Key benefits*: Antioxidant protection against multiple free radical pathways, modulation, and regulation of inflammatory markers, and treatment of photodamaged skin.
3. *Primary adverse effects*: None known.
4. *Practical applications in dermatology*: May be useful in treating photodamaged skin.

Cell Signaling: Amino Peptides

1. *Science and clinical studies*: Amino peptides are chemically linked to Palmitic Acid to enhance solubility allowing the peptide to become non-polar to cross lipids bilayers. Palmitoyl Pentapeptide-3, tested in a six-month clinical study, demonstrated improvement in the visual appearance of wrinkles by possibly stimulating fibroblast to rebuild the extra-cellular matrix and induce collagen synthesis. Palmitoyl Tetrapeptide-3 is said to control the secretion of cytokine (IL-6), delaying the effects of premature aging. Recent studies have shown that Palmitoyl Tetrapeptide-3 can make a substantial difference in the appearance of stretch marks. In one study, 93% of subjects showed a marked improvement in the length and depth of stretch marks and wrinkles. In addition, there was a substantial improvement in the skin smoothness and tone. Similarly, Acetyl Hexapeptide-3 is thought to reduce wrinkles by disrupting the nerve signals sent

to tense muscle beneath the dermis—functionally relaxing them and smoothing the overlying skin.
2. *Key benefits*: Collagen and glycosaminoglycan stimulation, inhibition of cytokines, disruption of nerve signaling.
3. *Primary adverse effects*: None known.
4. *Practical applications in dermatology*: May be useful in treating photodamaged skin.

Cell Signaling: Copper Peptides

1. *Science and clinical studies*: Benefits of copper peptides for tissue regeneration were discovered in the 1970s. Copper peptides have been shown to be effective in healing wounds and skin lesions as well as some gastrointestinal conditions (36). A double-blind, placebo-controlled study demonstrated that topical application of a copper peptide cream accelerated the rate of skin healing and reduced irritation after both irritant and allergic contact dermatitis. Although the primary area of studying copper peptides relates to wound healing, there has been some research implying that the complex has anti-inflammatory and antioxidant functions.
2. *Key benefits*: Cell signaling, wound healing, may have anti-inflammatory and antioxidant activity.
3. *Primary adverse effects*: None known, well tolerated.
4. *Practical applications in dermatology*: Acceleration of wound healing and may serve as an alternative to patients who are cannot tolerate retinoids.

Cell Signaling: DHEA

1. *Science and clinical studies*: DHAE and the sulfated conjugate (DHAE-S) are abundantly produced human adrenal steroids which become minimized with age. These materials relate to skin aging through the regulation of and degradation of extra cellular protein. DHEA has been shown to increase procollagen synthesis and inhibit collagen degradation by inhibiting metallo-proteinase (MMP-1) and increase tissue inhibition of MMP (TIMP-1) in dermal fibroblasts. Inhibition of cellular damage caused by UV exposure is thought to be due to inhibition of AP-1 activity. DHAE was also found to induce growth factor-beta 1 and connective tissue growth factor mRNA in cultured fibroblast. In a four-week study, a 5% DHAE mixture was applied to buttock skin three times a week to volunteers and produced a significant increase in the expression of procollagen alpha 1 mRNA and protein in both young and old skin and significant reduced basal expression of MMP-1 mRNA and protein, but increased TIMP-1 protein in aged skin.
2. *Key benefits*: Increase collagen synthesis, decrease MMP-1, and increase TIMP-1 to enhance collagen production and minimize collagen breakdown.
3. *Primary adverse effects*: None known.
4. *Practical applications in dermatology*: May be useful in treating photodamaged skin.

Cell Signaling: DMAE

1. *Science and clinical studies*: DMAE is considered a tertiary amine and a precursor of choline. At concentration of 1% to 5% when applied to facial skin, DMAE have been shown to produce and increase tone in about 20 to 30 minutes. Half-and full-face studies applied over 16 weeks to one year have been shown to produce periorbital tightening as well as tightening in the molar and mandible regions. These results appear to reverse when product application is stopped after eight weeks (36).
2. *Key benefits*: Enhances muscle tonality and can act as a penetration enhancer.
3. *Primary adverse effects*: Low toxicity and no side effects.
4. *Practical applications in dermatology*: Non-surgical treatment to correct loss facial anatomic positions.

HOW TO SELECT THE "BEST" FORMULATION OF A COSMECEUTICAL

Stability

Most companies do not state if a product is stable or how long it will last either opened or unopened, with the exception of OTC products, which are expiration dated if they do not last more than three years. However, international cosmetic and/or cosmeceutical companies marketing in the EU are required to put an expiration date on products if they do not last for at least 30 months. Most recently, the EU has instituted in law that companies must now include an icon of an open jar with the number of months that the product is good for after it has been opened (Fig. 2). The latter is the best way for the consumer and skin care professionals to determine how stable a product may be. Although this regulation has become effective as of March 2005, it will eventually appear on domestic products manufactured by international marketing companies. With the exception of waiting for this system to come into practice in the U.S., the only other way to determine the stability of a product not expiration dated would be to call the manufacturer directly and ask.

36M on or near the open jar icon (below) would represent the number of months that a product is stable (in this case, 36 months or three years) after it has been opened. This number and icon must be present on both the product container as well as the box (if applicable) that it is sold in. At this time there is no standard for testing or minimal

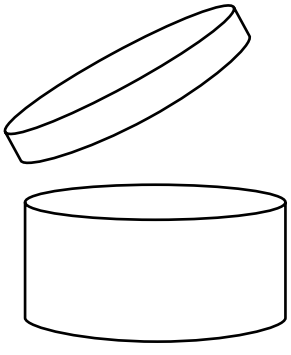

Figure 2 Example of period after opening (PAO) icon.

requirements that a product most be stable for in order to be marketed; however, it is expected that guidelines will follow shortly.

Efficacy

With the age of computers and Internet access, the best and easiest way to evaluate the efficacy of a product is to run a simple Internet search using an engine similar to Google (http://www.google.com). More advance searches may be conducted using various databases like PubMed (http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?DB=pubmed). The latter will be more specific; however, remember that not all manufacturers publish data in peer-reviewed scientific journals. Short of running your own database searches, the only other way to obtain this information is to call manufacturers directly and request copies of any data they have on file.

Science vs. Science Fiction

Although it would be great to be able to find all the information you want in a straightforward peer-reviewed journal search, it is highly unlikely. The basic information that is obtained from an on-line database like Google will have a great deal of marketing hype with little to no science. However, it may not be a bad place to at least start to learn some basic information prior to contacting a manufacturer for additional information.

Value

With the cost of cosmeceuticals escalating to as much as $500 per ounce, it is extremely difficult to determine how to advise patients. First and foremost are questions of efficiency and safety. Is the product effective at all? Is it effective for each of the claims? Is there well-controlled statistically significant claimed data to substantiate these claims? How effective is the product relative to other effective products (OTC or Rx)? What is the relative cost to the patient compared to other available and effective products? Would you purchase this product using your own money for use on your own family?

THE FUTURE OF COSMECEUTICALS

Our knowledge of the cellular signaling pathways is growing by leaps and bounds due to advances in gene microarray analysis and other genomics and proteinomic discoveries. These are being rapidly translated into practical applications for skin care. The ability to understand the molecular biology associated with the development and maintenance of the skin's structure and function is vital to the future of scientifically sound skin care.

As we learn more about how the skin interacts with the environment around it and how it responds to injuries, we will see significant advances in therapies. There are vast numbers of botanical products available to evaluate which produce many unique molecules. Some of these are part of the plant's defenses against their environment and have applications for our skin as well. The ability to synthetically manufacture some of these complex compounds has expanded greatly in recent years, and the future is bright for our ability to not only copy but also to create new analogs and derivatives of such compounds.

The impact of free radicals/ROS on the skin and how to neutralize or control this at an early stage as ROS are initially generated will lead to more "preventive/defensive"

products and, with proper public education, hopefully a more proactive approach to skin care. This is the true "anti-aging"—much of current therapies are still focused on "age reversal" or repair rather than preventive therapies. The cascade of cellular events and damage triggered by free radicals and the negative impact of chronic upregulation/activation of degrading enzymes and chronic inflammation in the skin contribute greatly to "premature" aging. The years ahead will see more emphasis on "beauty maintenance" or "skin fitness for life" as products and actives and delivery systems become more scientifically sound.

The large pharmaceutical companies may begin to play a more significant role in cosmeceutical development as the ability to use cosmeceuticals for drug-like effects allows them to utilize their resources to develop effective new skin care products without some of the regulatory burdens and costs associated with drugs. The time delay from new discoveries to actual products available for consumer use can potentially be dramatically reduced by this pathway.

Single Nucleotide Polymorphism (SNP) testing via a mouth swab may well play a role in determining long-term skin care plans/needs for people in the near future as this testing becomes more available. Correlations of testing results with actual clinical needs based on solid science and clinical studies will be a challenge since this database will need to be developed. However, the ability to look at one's "variation" from the "normal" population in SNP could provide very useful insights into skin care.

Major breakthroughs in photoaging and repair of DNA damage and telomere repair appear to be imminent. Genetic engineering is still a struggling infant but can become a giant in skin care in the future. Hormonal regulation and immune function issues with the skin will be more important in the future. Much of what we were taught was "intrinsic aging" and thus not alterable by medicine and science will soon be able to be manipulated at some level—only time and some core genetic issues will be immutable. Treatments that were unthinkable a few decades ago will become a reality, and cosmeceuticals or their derivatives may well play a role in this area of medicine. The use of low intensity light to photomodulate skin cells and/or to activate or interact with topical cosmeceutical agents may also enter the market place.

Marketing claims will likely continue to push the edge of the envelope. It is unclear if or when (and at what point) the FDA may intervene in this arena, but this too bears watching closely. The science needed to support the claims is sadly absent in many cases, but there are also some stellar examples of great science and clinical studies for cosmeceuticals and this trend is growing. Hopefully we will see some new standards set in this industry for science and data that will allow us to discern what benefits are real and which products deliver them. However, in the short term it is likely that the current confusion in the marketplace will continue or perhaps worsen so education will be the key. Dermatology residency programs need to increase their training related to cosmeceuticals so that dermatologists are not left behind and maintain their tradition of being the true "skin care experts" and the best resource for consumers who need guidance in planning their skin care regimen. Dermatology needs to take a strong leadership position in cosmeceutical research and development as well.

Hopefully the near future will see more science and less "science fiction" in research and marketing claims for cosmeceuticals. The issue of hype versus hope versus reality is a very real one for contemporary advertising. The ability to harness the power of natural products and their derivatives for treating skin diseases and for anti-aging purposes is about to undergo giant leaps forward as genomic research gives us new understanding of the structure and function of the skin—and also provides much more accurate ways to

screen for active compounds and produce optimal formulations. Cosmeceuticals are the wave of the future in science-based skin care.

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