Evolution of Cosmeceutics and Its Application to Skin Disorders Including Aging and Blemishes

Des Fernandes
The Renaissance Body Science Institute, Cape Town, South Africa

INTRODUCTION

From time immemorial, people have tried to maintain healthy skin or treat skin problems with topical applications of mud, urine, animal products, oils, plants, or plant extracts and resins, and others. All of these were virtually ineffective except mud applications, which did have the advantage of providing UV protection. Generally, cosmetics developed into applications of colored substances on the skin to disguise the problems beneath. With time, simple creams came into use and with them a burgeoning industry that today makes a fortune in selling creams, gels, and other topical products largely produced from inexpensive ingredients such as simple fats or oils and emulsifiers or gelling agents, with colors and added perfumes to disguise the natural smell. The industry was built on selling “hope in a jar” because the most that these products could do was to create a surface barrier or oil that would inhibit the natural loss of water through the epidermis and thereby alleviate dry skin. Mesmerizing advertisements to promote the latest magical ingredient that promised eternal youth and beautiful skin were the only effective ingredients in the whole package. There has never been a shortage of gullible buyers, and so the cosmetic industry eventually developed into an industry driven by seductive titles and fanciful packaging containing ineffective serums or creams laden with inviting colors and perfumes.

Fortunately, we now live in a new age because scientific research has shown us that real science can be included into the cosmetic pot to make positive changes to skin. The creams containing these active scientifically proven ingredients are called cosmeceutics and have now become the key driver in the cosmetic industry. The cosmeceutic market in the first world was valued at about US$20 billion in 2005 and may top US$30 billion by 2010 as more and more men and women try to make a difference to their aging skin.

THE ORIGIN OF THE CONCEPT OF COSMECEUTICS

The cosmetic industry entered a phase of transition in the last quarter of the 20th century when Albert Kligman, a U.S. dermatologist, coined the term cosmeceutics to describe a new form of cosmetic based on essential micronutrients to gently nurture and rehabilitate photoaged skin. Cosmeceutics are not simply a traditional cosmetic but a skin care system that include active ingredients that create physiological changes in skin cells to make skin appear younger and healthier. Topical medications had helped us to understand that the epidermis was not a total barrier, and one could influence the state of the skin by applying various medications such as cortisone and antibiotics. The next step that led to the concept of cosmeceutics was the realization...
that wrinkles, pigmentation blemishes, and other signs of photoaging are not simple
“conditions” of normal skin and a natural effect of getting older but are in fact varying
degrees of a serious skin disease. They are merely the earliest signs of actinic
damage of the skin that eventually leads to the development of solar keratoses and
skin cancer. The recognition of wrinkles and pigmented blemishes as a disease is a
major philosophical and physiological step that many clinicians have great difficulty
in taking. Photoaged skin is diseased skin and needs to be treated with appropriate
products. Treatment of the early signs of sun damage is quite clearly preventive
medicine, and so one really needs “medicines” to deal with the problem. This is
where cosmeceutics come into the picture. We need active cosmetics that have a
therapeutic effect on the skin. The word cosmeceutic conveys the meaning of cosmet-
icics that have a pharmaceutical effect in the same way as topical medicines, and this
word introduced a revolution in skin care.
Cosmeceutics have become a household word and also one of the most misleading
words in the cosmetic industry, which has seized on the term and realized
another successful marketing myth. Clearly, to claim that a product is a cosmeceu-
tic, it has to fulfill three important conditions:

1. It has to include scientifically proven active ingredients at concentrations that
   have physiological effects and make observable improvements of human skin.
   The effects would be
   • reduction of fine lines and wrinkles,
   • thickening of the epidermis,
   • increased, normal collagen network,
   • improved elastin deposition,
   • restoration of natural moisturizing factors,
   • normalization of skin color and removal of pigmentation blemishes, or
   • normalization of sebum secretion.

2. A cosmeceutic should be formulated to give optimum penetration of the active
   ingredients. A product with adequate concentrations of effective ingredients
   will not work as a cosmeceutic if the formula does not ensure good penetration
   of those ingredients to the area where they are needed. In some cases, transder-
   mal penetration has to be enhanced to position the active molecule where it is
   most needed.

3. A cosmeceutic should not expose the client to any deleterious consequences,
   although one has to realize that because effective concentrations of active in-
   gredients are used, the possibility of transient skin reactions does increase.
   This is in keeping with the Gauss distribution curve. Inevitably, some people
   may develop skin irritation, whereas most get good changes or even superb
   changes to their skin. For that reason, cosmeceutics should only be adminis-
   tered by trained skin care therapists who can advise clients on better ways
to use them, and ideally cosmeceutics should not be sold over the counter in
department stores and others.

This chapter should only deal with agents that are considered cosmeceutic. Most
physicians interpret cosmeceutics as glycolic acid and other α-hydroxy acids (AHAs),
but in fact they have rather small cosmeceutical effects on skin cell physiology. Gly-
colic acid has minimal effects on skin cell metabolism and acts mainly as an abrasive
type of agent that works mainly on the stratum corneum and sheds the superficial cor-
neocytes. Its effects on collagen formation are related to its peeling properties, and if glycolic acid is supplied as glycolates at a more physiological pH (about 4.5–6.5), then there is minimal observable impact on the skin. The main impact of AHAs on skin is as a peeling agent and not as a cosmeceutical. Very largely, AHAs are impostors in the field of cosmeceutics, although they do have observable effects on photoaging. There are far more worthy cosmeceutic ingredients that AHA when treating photoaging.

THE SIGNS OF PHOTOAGING

Tanned skin is so common that people fail to recognize that it is the first sign of photoaging. Tanning occurs because DNA has been damaged by UV light, and this induces the release of nitrous oxide, which initiates the production of melanin. The horny layer is thickened, and this may make the surface feel rough. Most of our photodamage occurs before the age of 20 years, and young patients are often shocked to hear that they already manifest the earliest signs of photodamage. The signs of photoaging are attributable to damage to each of the four important cells in the epidermis and dermis and to the blood vessels and structural proteins in between the cells. In the epidermis, these are the (1) keratinocytes, (2) melanocytes, and (3) Langerhans cells, and in the dermis, the (1) fibroblasts, (2) collagen and elastin, (3) water-retaining substances between the cells, and (4) blood vessels.

Changes in the Epidermis

The keratinocytes and keratinocyte stem cells may produce clones of abnormal cells of varying size, pycnotic nuclei with abnormal DNA, and an irregular growth pattern. They contain more melanin granules, and this is the first easily detectable sign of photoaging. Irregular clumps of pigmentation are observed instead of the normal even distribution of melanin. UV irradiation promotes the release of active substances from the keratinocyte that promote the production of melanin in the melanocytes. Altered keratinization of the dermis results in a thickened rough skin, which leads to an impaired barrier (stratum corneum) and, subsequently, dry skin. With progressive sun damage, the basement membrane and the rete pegs are affected, and the epidermis becomes thin and atrophic with flattened rete pegs. There is a loss of the fine fibers anchoring the epidermis to the basement membrane and dermis. DNA damage, if unrepaired, leads to actinic keratoses and may progress to basal and squamous cell carcinomas.

Langerhans cells are responsible for immune functions of the skin and would normally detect cells that have undergone DNA damage and mutation. However, Langerhans cells are also susceptible to UV irradiation, and as a result, these aberrations are not detected and clones of abnormal keratinocytes and melanocytes may proliferate (1). Irradiated Langerhans cells have fewer Birbeck granules and lose their dendrites, and when they are impaired, the following clinical conditions may occur:

- Solar keratoses develop in irradiated skin and may progress into skin cancer.
- Skin allergies become more common.
- Patients are more prone to skin infections.

Melanocytes are responsible for melanin production and abnormalities result in the following:

- Tanned skin in the short term. The DNA of melanocytes may mutate to produce much more melanin than normal. Each melanocyte supplies melanin to its
melanocyte unit of about 36 to 40 keratinocytes and sometimes to fibroblasts. These melanocytes slowly form a clone of hyperactive cells. Although the change may only be detectable initially with the Woods light, later on, this will manifest as typical mottled aged skin, but, if you catch this early on and treat it properly, then you can avoid it.

- Irregular pigmentation blotches may develop and coalesce into melasma. In some people, particularly in darker skinned people, ugly pigmentation blemishes may occur on the main sun-exposed areas of the face, which are particularly resistant to treatment. This poses one of the most difficult problems that we have to deal with among Asian people and creates a special value for cosmeceutics.

- Although exposure to sunlight seems to play an important part in the development of melanoma, the exact causes are still unknown.

Changes in the Dermis

Fibroblasts produce less matrix substances of the dermis, which promote the manifestation of wrinkles. The delicate skin of the lower eyelid may be the first area to show damage. Wrinkles may be because of a loss of the anchoring fibrils below the basement membrane (2). These are composed of type VII collagen, and they are destroyed by matrix metalloproteinase 2. Normal structural collagen of the dermis is also destroyed by light. Collagen mRNA is down-regulated, and with increased metalloproteinases, this results in a net loss of collagen, which is also damaged by UV light (3).

Elastin, by contrast, is formed in greater quantities, but the elastin fibers become thickened instead of forming a healthy fine mesh to support the skin. Elastin fibers are fractured by UV light, and they roll up into little balls that can be seen quite easily on the neck skin in even only moderately sun-damaged people. As a result of defective action of elastin and diminished support from collagen, the skin starts to sag. In addition, there is less glycosaminoglycans and other water-retaining molecules in the skin, and so the skin becomes dry. Solar irradiation damages the collagen support around blood vessels and causes dilation of these vessels. Poor circulation shows up as a sallow, poorly nourished skin.

UNDERSTANDING THE MECHANISMS INVOLVED IN THE PRODUCTION OF PHOTOAGED SKIN TO DESIGN COSMECEUTIC PRODUCTS

We have to understand the mechanism of solar damage to mount a scientific attack on photoaging. The simple acceptance of photoaging as a condition endured by aging people is incorrect because clinicians will then follow irrational marketing advice and, in ignorance, suggest “cosmeceutic” products containing AHAs, such as glycolic acid, instead of recommending a focused cosmeceutic product. We have to know how light, particularly UV light, damages skin. Light consists of a spectrum of photons, which are “packets” of energy that vary according to the wavelength. Essentially, light enters into the skin and certain wavelengths of light (photons) can damage the skin by either interacting on the molecular level with chromophores to changing their chemical structure or on the subatomic level by creating free radicals. Most people believe that the damage is done by UV light only, but in fact, even green, blue, and violet light can damage cells. Few people are aware that even “soft” green light can damage keratinocytes sufficiently to stimulate melanocytes to make more melanin! Because the production of melanin is only induced
by damage to the keratinocytes’ DNA, every “beautiful” tan is in fact evidence of photodamage.

Skin Chromophores

On the molecular level, a photon’s energy can be absorbed into the molecule, which is then altered. In some cases, this interaction causes heat (e.g., when light interacts with melanin) or light (photoluminescence) or the chemical nature of the molecule may be altered. This is the change that interests us most, and the prime example of this is vitamin A. When vitamin A molecules (particularly retinyl palmitate) absorb the energy of photons in the range of about 334 nm, the increased energy changes the structure of the molecule, and vitamin A activity is lost. As a result, a localized deficiency of vitamin A and other photosensitive molecules develops after exposure to sunlight.

The chromophores for UVB are melanin, DNA, urocanic acid, vitamin E, advanced glycation end products and 7-dehydrocholesterol. Melanin does not, in general, pose a problem because it absorbs energy and will only create heat and absorbs any free radicals as well as chelating heavy metals.

DNA absorbs UVB at about 260 nm, and this damage deserves special attention because this will cause malfunctioning of cells and important mutations. Urocanic acid is among the normal oils secreted by the skin and acts as a natural sunscreen; however, when it absorbs UVB energy, it becomes cis-urocanic acid, which promotes suppression of the immune system and can promote the development of skin cancer. Vitamin E becomes inactivated by absorbing UVB rays. Proteins modified by advanced glycation end products can damage DNA. Advanced glycation end products accumulate on long-lived skin proteins such as elastin and collagen as a consequence of glycation. Advanced glycation end product proteins collect in the nucleus as well as the cytoplasm. DNA strand breaks occur from increased free radical activity as well as direct electron transfer between photoexcited advanced glycation end products and DNA. So as we age, we produce potent photosensitizers that make us age even more and cause more DNA damage! Not all chromophore interactions are damaging: an example is 7-dehydrocholesterol, which absorbs UVB energy and is converted to vitamin D in the keratinocytes.

On the other hand, UVA damages DNA through free radical action rather than absorption of energy by a chromophore. UVA rays are ubiquitous, plentiful, and can penetrate through clouds and window panes, so it is easy to understand that vitamin A in the skin is easily denatured by exposure to light. However, vitamin A is damaged because it is a chromophore and becomes inactive and cannot be reconstituted. In a paradoxical twist, UV light may also assist isomerization of all-trans-retinoic acid to cis-retinoic acid, which are both ligands for the genes expressing the effects of vitamin A. UVA, in addition, can activate genes at very low doses, and we experience this when we are trying to treat pigmentation problems. Very low-intensity light could activate the mechanisms responsible for inducing melanin production by melanocytes. Melanin absorbs UVA rays and all other light rays without damaging cells. NADH is important to the cells of our skin because it is a source of energy and gets altered into an inactive agent by absorbing UVA energy. Glutathione is an important antioxidant but depleted by UVA and that leads to a sensitization to UVA 334 nm (which inactivates vitamin A) and 365 nm and near-visible blue-violet light (405 nm, which inactivates vitamin C), as well as UVB 302 and 313 nm. Another paradox is that vitamin D is also sensitive to light and
photodegrades easily once it has been formed in the skin. For this reason, people
should not stay in the sun much longer than 20 minutes if they are intent on mak-
ing vitamin D. Riboflavin and tryptophan both absorb UVA and, as a result, can
increase the formation of free radicals.

Vitamin C (ascorbic acid) is a chromophore that is not affected so much by
UV light (except in the battle against free radicals) but rather by blue light, which it
absorbs and becomes deactivated.

The Role of Free Radicals in Photoaging

On the subatomic level, the absorption of energy can also result in electron changes
with the generation of free radicals. If a photon should strike a vulnerable paired
electron in the outer circuit of an oxygen atom, the electron is cast out of its circuit,
and the molecule, in its quest for another electron, becomes a free radical. A free
radical is in fact simply an atom with an unpaired electron that starts up a destruc-
tive concatenation of chemical reactions, involving tens of thousands of molecules
in a fraction of a second, which may end up with damage in the cell membranes
or in the DNA of the cell. We must never forget the dangers of uncontrolled free-
radical activity, so we should always ensure that our skin is rich in a wide variety
of lipid- and water-soluble antioxidants. They have to be included in the skin care
regimen and should be used both day and night.

FOCUSING ON CHROMOPHORES AND FREE RADICALS
IN DEVELOPING COSMECEUTICS

We know that only sun-damaged skin photoages. By understanding the chemical
changes induced by exposure to sunlight, we can deduce that the most likely cause
of photoaging is a chronic deficiency of essential chromophores in the exposed skin
combined with the effects of free radicals. Clearly, by understanding which mol-
ecules in skin are damaged by light, we should be able to design a cosmeceutic
regime to combat photodamage and reverse its effects. The first molecules to come
to mind are vitamins A and C, which could be described as the major vitamins of
healthy skin.

For decades, we have realized that vitamin A is vital for healthy skin. Wise and
Sulzberger (4) worked with vitamin A and realized that it was extremely unstable in
light, and they suggested in 1938 that there is a local hypovitaminosis A in wrinkled
skin. We now know that UVA rays, particularly at 334 nm, are responsible for photo-
decomposition of retinyl palmitate that is the main storage form of vitamin A in the
skin (5). The plot thickens because we also know that vitamin A is the one key mol-
ceule essential for the normal growth and differentiation of all the important cells
of the skin: keratinocytes, melanocytes, Langerhans cells, and fibroblasts. Cluver (6)
was a pioneer in recognizing that vitamin A played an essential role in counteracting
sun damage. He showed that every time we go out into sunlight, the photosensitive
vitamin A molecule is denatured not merely in the skin but also in the blood. With
time, investigations have demonstrated that vitamin A is not only good for aging
skin but is actually essential. Women have an added disadvantage because blood
levels of vitamin A drop when they menstruate (7). This means that skin levels are
also lower, and so they are more vulnerable to photodamage during menstruation.

Retinyl palmitate, but not retinol, absorbs UV energy. Retinol is protected by
its bond with a specific retinol-binding protein (8). A recently recognized effect of
adequate doses of retinyl palmitate specifically within skin cells is to reduce the
production of thymine dimers in the DNA. According to Antille et al. (9), “In human
subjects, topical retinyl palmitate was as efficient as a sun protection factor 20 sun-
screen in preventing sunburn erythema as well as the formation of thymine dimers.
These results demonstrate that epidermal retinyl esters have a biologically relevant
filter activity and suggest, besides their pleomorphic biologic actions, a new role for
vitamin A that concentrates in the epidermis.”

Vitamin A has a vast array of hormonal, physiological actions on the cells of
the skin but is not (for practical purposes) an antioxidant, whereas vitamin C has
some hormonal role on the DNA of the fibroblast by activating about four genes
responsible for collagen production. It also has effects on the melanocyte by provid-
ing a reducing milieu to reduce the formation of melanin, but its main action is as an
important antioxidant. Vitamin C is important for the reactivation of vitamin E that
has been converted into a tocopherol radical by quenching a free radical. Vitamin E
plays an essential role as an antioxidant in safeguarding cellular membranes, and
when it is applied topically, it augments photoprotection; however, this advantage
only becomes clear a day or two after sun exposure. Patients using topical vitamin E
get less sunburn and a lighter tan. Vitamin E is also light-sensitive and can be oxi-
dized into an inactive form. Vitamin E, on the other hand, seems to have virtually no
metabolic action at all and is only an antioxidant in the lipid phase of the cell.

This localized deficiency of vitamins A and C and skin antioxidants is insidi-
ous. Not all the vitamin A in the skin is destroyed, but it is instantaneous, and a
single UV exposure could lower the levels of vitamin A in the skin where UVA
can penetrate by 70–90% (10). The skin cell stores of retinyl palmitate are progres-
sively diminished. Because retinoic acid is required for the formation of retinoid
cellular and nuclear receptors, fewer retinoid receptors are produced on the cell
membranes, and the retinoid metabolic pathways become less efficient. The kera-
tinocytes produce less of the essential keratins and ceramides that ensure an ef-
teffective chemical barrier for the skin. The horny layer becomes much thicker and
rougther, with a basket-weave pattern instead of being compact, thinner, but denser.
Rounded keratinocytes release the precursors of matrix metalloproteinases (col-
lagenases, elastases, and gelatinases). Normally, vitamin A controls the conversion
of pre–matrix metalloproteinases secreted by keratinocytes and fibroblasts into ac-
tive matrix metalloproteinases, but with a deficiency of vitamin A, UV irritation
stimulates the unimpaired release of metalloproteinases that then destroy collagen
and the anchoring fibrils. Without vitamin A, the rete pegs become flattened. Langer-
hans cells need vitamin A to function, but if the vitamin A is inactivated by light,
then they cannot function properly and recognize cells whose DNA has been dam-
aged. These cells would normally be removed but clones of abnormal cells slowly
start to develop and, years later, manifest as keratoses or skin cancer.

The melanocyte is stimulated to produce more melanin, but if there is ad-
quate vitamin A, this is controlled for unexplained reasons, and the distribution
of melanin in the skin is kept even. If the DNA of the melanocyte is damaged by ir-
radiation, excessive amounts of melanin may be produced under lower light fluxes.
These clones of cells are also not recognized by the Langerhans cells and grow into
obvious splodges of darker pigment that are very resistant to treatment.

The fibroblast produces less glycosaminoglycans, so the skin feels drier, and
wrinkles show up very easily. There is little value in looking at diet to replenish the
depleted vitamin stores because that will take too long. Once the skin retinoids are
depleted after a heavy exposure to sunlight, it takes several days before diet alone
can restore the normal cutaneous retinoid levels (5). On the other hand, application
of an active vitamin A cream can restore the normal levels within hours.

Ascorbic acid is water-soluble and is not stored in cells, so loss has to be re-
placed by the blood supply. Deficiencies of vitamin C permit more free radical dam-
age but this does not show up clinically until significant damage has been done.
There are no cellular receptors for ascorbic acid probably because its main action is
as an antioxidant in extracellular fluid where it is closely associated with lipid mem-
branes and can easily interact with vitamin E. Melanin is produced under oxidative
conditions, so low levels of vitamin C would favor the development of pigment
blemishes.

Vitamin E (\(\alpha\)-tocopherol and derivatives) is probably the major antioxidant
in the skin and is readily depleted after sun exposure (11). The normal network
antioxidants of the skin are vitamin E, vitamin C, glutathione, coenzyme Q10, and
\(\alpha\)-lipoic acid. These are potentiated by flavonoids and carotenoids. Betacarotene,
the plant form of vitamin A, is a powerful free radical quencher. Estimates suggest
that one molecule of betacarotene can cope with 1000 free radicals. Lutein is another
carotenoid that has particular value because it is a powerful absorber of blue light,
which can severely damage cells. There are many other carotenoids that can also
protect the skin. Sun exposure seriously depletes the levels of these essential anti-
oxidants (12), so we are impelled to boost our antioxidant protection both topically
and systemically. Panthenol is a coenzyme in fat and carbohydrate metabolism. It
has other soothing effects on skin and is also a free radical quencher.

SELECTING COSMECEUTIC INGREDIENTS

Cosmeceutic ingredients should be classified as

- those that are naturally found in the skin (e.g., chirally correct vitamins);
- phytonutrients not normally found in skin but have physiological benefits (e.g.,
green tea polyphenols);
- designed molecules (e.g., peptides not normally found in nature but that have
physiological actions due to their cytokine activity).

SCIENTIFICALLY PROVEN COSMECEUTIC INGREDIENTS

Although it is not feasible to make an encyclopedic list of all known cosmeceuticals,
we can concentrate on the most widely used cosmeceuticals, which are briefly given
here.

Vitamins and Antioxidants

Vitamin A, as retinoic acid, retinol, retinyl aldehyde, and retinyl esters, was the
first cosmeceutic ingredient that was brought to our attention. Kligman had been
researching the treatment of acne with retinoic acid (vitamin A acid, or tretinoin)
in the 1960s, and over time, he noticed that his patients developed healthy skin. By
1986, he was able to report for the first time in history that a topically applied prod-
uct had reduced wrinkles (13). This report was followed by another landmark paper
under the guidance of Voorhees (14).

It has been established that a chronic deficiency of vitamin A lies at the heart
of photoaging. We also know that vitamin C (ascorbic acid and its water and lipid-
soluble variants) deficiency aggravates the effects of vitamin A deficiency as far as 
collagen and melanin are concerned. Because vitamins A, C, and E (tocopherol) 
and other network antioxidants [carotenoids, flavonoids, coenzyme Q10 or ideben-
one, dehydroliopic acid (α-lipoic acid), green tea, peptides, AHAs, and β-hydroxy 
acids (BHAs)] are the fundamental molecules that determine the development or 
repair of actinic damage to create a function cosmeceutic for photoaged skin, one 
has to include topical replenishment of these vitamins. Of course, prevention is 
better than cure, so we should start using these vitamins on our skin from a very 
early age. I believe that we need to dose skin with vitamin A and the associated 
antioxidants very soon after we are first exposed to sunlight and to keep doing so 
for the rest of our lives. This means that the skin will never suffer from transient 
deficiencies of vitamins A and C and become more resistant to the development of 
skin cancers.

Which vitamin A? Medical literature reports for retinoid replenishment of the 
skin are virtually confined to retinoic acid despite the fact that there are a number of 
other chemical forms of vitamin A. In 2000, Voorhees reported that a cosmetic ingredi-
ent (retinol) was able to minimize photoaging (15). Saurat et al. concentrated on reti-
nyl aldehyde (16) because retinyl aldehyde is one metabolic step away from retinoic 
acid, and although it is a cosmetically approved ingredient, its structural proximity to 
retinoic acid would give it an added advantage over retinol. Retinoic acid is generally 
classed as the medicinal form of vitamin A because of its rather harsh topical effects. 
All-trans-retinoic acid and some of its isomers are the ligands that interact with the 
DNA, but the fact remains that retinoic acid is not usually found extracellularly. Topi-
cal applications of retinoic acid do raise the levels of retinoic acid in the skin, but at 
the same time, the retinyl palmitate levels are also increased probably because of the 
reduction of the conversion of retinyl palmitate to retinol and retinaldehyde. Retinoic 
acid is irritant to skin and causes a marked retinoid reaction if there are inadequate 
retinoid receptors on the cell walls. Normal cellular physiology favors only minute 
quantities of retinoic acid within cells. Retinyl esters can be converted to retinol, then 
to retinyl aldehyde, and finally to retinoic acid. The step from retinyl aldehyde to 
retinoic acid is not reversible, so whatever retinoic acid is presented to the cell, it has 
to remain as retinoic acid and be metabolized and interact in the nucleus as the ligand 
for retinoid acid receptors (RAR and RXR and their subtypes). Should there be more 
than the cell can use, it cannot be stored as a retinyl ester. On the other hand, retinol 
and retinyl aldehyde are easily converted to retinyl esters. It also seems that the larger 
the retinyl ester storage, the higher the levels of retinoic acid. Retinyl esters may in 
fact be the driving force in the metabolism of vitamin A. That means that one does 
not have to use retinoic acid to get the effects of retinoic acid (17). Applying retinyl 
aldehyde or retinol, or retinyl esters such as retinyl palmitate or retinyl acetate to the 
skin will give similar results to retinoic acid but at physiological doses of retinoic acid. 
However, investigation has shown that when retinol or retinyl aldehyde is applied to 
the skin, then virtually all is converted to retinyl esters, and very little is converted to 
retinoic acid. If you scan the cosmetic advertisements, then you will get the impres-
sion that the only version of vitamin A that works is retinol. However, retinol is ir-
ritant to cell membranes and is normally found free only in tiny doses in the skin. It is 
the form used for transport of vitamin A from the liver, through the blood to the body. 
However, virtually all the retinol applied to skin will be converted to retinyl palmitate 
and build up the stores of vitamin A in the skin cells (18).

Retinaldehyde advertisements focus on the fact that it is only one step away 
from retinoic acid and imply that it is a simple step to the active version of vitamin A.
However, once again, enzymes convert virtually all the topically applied retinaldehyde into retinyl palmitate, and only a tiny fraction actually gets converted into retinoic acid.

The esters of vitamin A (e.g., retinyl palmitate or acetate) are milder, active, and more easily tolerated by the skin. Jarret (19) showed that retinyl acetate was similar but more active than retinoic acid (20), with fewer side effects.

We have to use the form of vitamin A that is easiest for our patients to use, and I believe that for initial stages, we should use retinyl palmitate because it is effective and will give all the effects of retinoic acid provided it is used in adequate concentration (21). For more intense treatments in patients who have adapted their skin to vitamin A, we can use retinyl acetate, retinaldehyde, or retinol. My experience indicates that although patients are reluctant to continue using retinoic acid daily, there is no problem with the continual use of retinyl acetate or retinyl palmitate. I have used retinol at higher doses, but not everyone can use it. Clinical experience has shown that retinol cannot easily be used at levels higher than 10,000 IU g%, whereas retinyl acetate and retinyl palmitate can be used as high as 50,000 IU g% both morning and evening for many years without any deleterious effects.

Which vitamin C? The ideal cosmeceutic care regime includes vitamin C (l-ascorbic acid), but it is unstable and rapidly decomposes. Ascorbic acid is commercially available as a dry powder (dehydroascorbic acid), which is relatively stable and white. When ascorbic acid powder is exposed to light and air, it slowly decomposes to oxidized ascorbic acid, which is brown. When ascorbic acid crystals are mixed in water, the solution fairly rapidly (over a period of weeks) decomposes to dehydroascorbic acid. Therefore, a solution of ascorbic acid, even in a gel, has a limited shelf life and should be used within 3 to 6 weeks. Ascorbic acid acts like an AHA, which interacts on the adhesion of the corneocytes and increases the penetration into the deeper layers of the skin. Ascorbic acid does not easily permeate the stratum corneum and passes with difficulty into the cell wall because it is a water-soluble molecule, and there are no receptors on the cell wall for ascorbic acid. However, magnesium (or sodium) l-ascorbyl phosphate is also water-soluble but is taken up into cells much more effectively. Inside the cells, the compound is readily converted to l-ascorbic acid, phosphate, and magnesium (sodium) (22). These solutions are also more stable than conventional ascorbic acid and can last up to 200 days before there is any appreciable loss of activity (23). Lower concentrations (compared with ascorbic acid) are required to get the same amount of ascorbic acid into the cell.

Ascorbic acid is too aggressive for people with sensitive skin, although they can use ascorbyl esters and, if the right dose is being used, will get more vitamin C into their cells. Patients with pigmentation problems should avoid any product that peels the skin because they need a thick horny layer to protect melanocytes. Ascorbic acid is an exfoliant, so I recommend that patients with melasma or other pigmentation problems should use ascorbyl esters. Better results may be achieved using an oil-soluble complex of ascorbic acid, ascorbyl tetraisopalmitate, which is extremely stable. This fat-soluble molecule passes more readily through the stratum corneum than l-ascorbic acid and achieves up to 10-fold more vitamin C in the cell. This leads to more effective control of melanin formation, greater collagen deposition, and more efficient antioxidant protection. Ascorbyl tetraisopalmitate combined with vitamin A gives rapid smoothening and lightening of the skin without any irritation. Of course, if it should also be combined with a wide antioxidant brigade and effective UVA protection.
Because vitamins A and E absorb UV light in the region that is responsible for most of its deleterious effects, both should be included when formulating a cosmeceutic. Topical vitamin A (in mouse skin) has been shown to prevent the UV-induced epidermal hypovitaminosis A, whereas topical vitamin E prevents oxidative stress and cutaneous and systemic immunosuppression elicited by UV. These natural epidermal vitamins A and E of the skin can be reinforced by topical application of natural retinoids and α-tocopherol (24). Botanical compounds, such as green tea (25), offer an expanding range of antioxidants that qualify as cosmeceuticals, and these are discussed elsewhere in this volume.

Surgeons are bombarded with claims about the magical effects of various products to rejuvenate skin. Because of the fundamental importance of vitamins A, C, and E and other antioxidants, if a skin care range does not include them, then it cannot claim to be true skin care. The burgeoning problem of stratospheric ozone depletion means that virtually everyone who ventures into sunlight will get more destruction of their cutaneous antioxidant system and, therefore, be at greater risk of photodamage. This may be the underlying reason for the dramatic increase in melanoma and other skin cancers. In ideal circumstances, everyone should apply vitamin A and other antioxidants daily and should wear sun protective clothing to maintain skin health.

There are cosmeceutic ingredients that are not involved in photodamage but can be used to rejuvenate cells or stimulate more collagen formation. Molecules that act on the mitochondria can correct senescent cells [e.g., idebenone, coenzyme Q10, dehydrolipoic acid (25)]. Coenzyme Q10 (ubiquinone) has the ability to prevent many of the detrimental effects of photoaging. The processes of aging and photoaging are associated with lower levels of antioxidants in mitochondria and an increase in cellular oxidation (26). Topical coenzyme Q10 was found to be effective against UVA and significantly suppressed collagenase in human dermal fibroblasts and reduced wrinkle depth (27). Coenzyme Q10, idebenone, and kinetin are not as effective in photoprotection compared with vitamins C and E (28).

**Active Peptides**

Recent research has shown that active peptides such as palmitoyl pentapeptide (Matrixyl®) and palmitoyl hexapeptide (Dermaxyl®) have a special value in stimulating the production of collagen and elastin. They are both made of a sequence of amino acids normally found in collagen and elastin. Palmitoyl pentapeptide stimulates about 16 genes in skin cells, which is only a fraction of the number of genes that vitamin A favorably stimulates in the skin. The peptides are not an alternative to vitamin A and should be used in conjunction with the vitamin. Copper peptides facilitate healing of tissues and may assist in remodelling of collagen. Probably the most appropriate indication for copper peptides is on skin injured by peeling, laser, or dermabrasion.

**AHAs and BHAs**

AHAs have been the most misused and misunderstood molecules in skin rejuvenation. They do have a role in smoothening skin, mainly as a peeling agent, but they should not be considered as true cosmeceuticals. AHAs are water-soluble and can only penetrate the outer stratum corneum unless higher concentrations are used to induce an acid peeling effect. They are effective in desquamating skin, increasing cell turnover, and stimulating keratinocyte growth.
AHAs modify the barrier function of the skin as their main function rather than influence the metabolism of the keratinocyte, and these changes are not the same for all AHAs but are more marked in those with antioxidant activity (29). An important concern about AHAs is that they may sensitize skin to UV damage. This, however, is transient and disappears on cessation of treatment (30).

Glycolic acid has been shown in vitro to stimulate the production of collagen (31). Epidermal and dermal remodeling of the extracellular matrix can result from high concentrations. Longer treatment intervals may result in collagen deposition as suggested by the measured increase in mRNA (32). These effects seem related to the concentration and low pH.

Lactic acid has great value in enhancing the natural moisturizing factors and is much kinder to skin than glycolic acid (33). Lactic acid does have effects on the metabolism of the cell, and even when supplied as lactates at a higher pH, they can still induce changes to skin by improving hydration. Lactic acid may also have an important role in stimulating the release of cytokines by keratinocytes (34). Lactic acid also inhibits tyrosinase and therefore reduces pigmentation. However, both glycolic and lactic acid are only modestly successful in reducing photoaging (35). They do impair the natural protection from the sun, and they should always be used in conjunction with vitamin A. Their role is more as an adjuvant than an actual therapeutic agent, except in the case of acne where they help to control infection and reduce obstruction of follicles.

Both AHA and BHA have effects on desmosomes and promote desquamation. BHAs may be more effective because they are lipid-soluble, penetrate the stratum corneum, and may penetrate into comedones. They also have the benefit of being more effective at lower doses.

Hormones
The advantages of using estrogen to thicken skin and recondition it in the menopausal phase are well-known. Vitamins cannot play the role of hormones and growth factors, so we have to use hormones when they are required, and hopefully future cosmetics will also include essential growth factors. At this stage, cosmeceuticals can only use phytoestrogens, but because these molecules do stimulate estrogen receptors, there is confusion about their use in patients with breast cancer.

CLINICAL USE OF COSMECEUTICS
Many surgeons make the mistake of believing that youthful skin can be achieved using drastic measures such as laser resurfacing, heavy peels, or other techniques that destroy the epidermis. Medical practitioners, in particular dermatologists, cosmetic, and plastic surgeons, should have an understanding of cosmeceuticals so that they can guide their patients in the use of effective cosmeceuticals to treat photoaging. Cosmetic surgery alone cannot create a convincingly youthful impression. The skin does not simply have to be smooth; it should look fresh, glowing, and show few or no signs of accumulated photodamage. Using scientifically targeted cosmeceuticals, one can normalize skin, and cosmetic surgery can achieve a more harmonious appearance as well as much more effective rejuvenation. An effective cosmeceutic will first restore normal function to keratinocytes. This usually results in healthier-looking skin, and results can match those achieved by more compli-
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Cated treatments (36). Unfortunately, even the most powerful cosmeceutic will not smooth skin as much as we wish it would, neither will melasma reliably disappear. For these reasons, we often have to resort to more major procedures to get the best results.

The first step is to use treatments augmented by enhanced penetration through the epidermis. We can enhance penetration by carefully formulating products so that more of the active ingredient gets down to the target areas, but this is not enough to obtain greater tightening of the skin and other positive changes. For greater penetration, one can use iontophoresis, low-frequency sonophoresis (LFS), or physical interference with the barrier properties of the stratum corneum (e.g., microneedling, microdermabrasion).

**Iontophoresis**

Galvanic current is useful if a selected molecule such as vitamin A or ascorbic acid can be ionized into positively and negatively charged ions. A charged electrical current repels similarly charged ions into the skin, the cells, and even right into their mitochondria. This can cause about 400% better penetration than simple topical applications. Treatments should be done for a minimum of 20 minutes once or twice a week for 24–30 treatments. This is a very successful method for treating photoaging but has to be done by an experienced therapist/nurse.

**LFS**

LFS uses sounds at about 20 kHz at an effective intensity to create cavitation of the lipid bilayers of the skin. Cavitation develops rapidly and is maintained for several hours after treatment. Adding treatments with LFS as described by Mitragotri (37) but adapted (Environ® Ionzyme® DF machine; Environ Skin Care, Cape Town, South Africa) for use in the skin care salon, up to 4000% better penetration may occur after only 3 minutes of treatment and quite dramatically rejuvenate skin (38). Of course, this will only happen if rational cosmeceutics are used. LFS should not be confused with ultrasound (about 1.1 MHz), which does not have the same powerful properties. The advantage of LFS is that it can be used on nonpolar molecules. Treatments are best done once or twice a week for about 24–30 times, and the best results seem to occur in combination with iontophoresis.

**Microneedling**

Microneedling of skin offers a means to enhance penetration. Holes are made only through the stratum corneum, so this is not painful, and patients are requested to use it daily before applying their skin care. Significant improvement may be achieved in those patients who are diligent about using the tool everyday for about 3–5 minutes. The results are because of enhanced penetration of vitamins A and C and other active agents, not microtrauma.

There are a number of other ancillary procedures to rapidly smoothen and lighten skin. The following treatments aim to induce tightening of the skin and/or lightening of the skin. They all work by controlled damage to either individual cells or all the cells of the epidermis or the dermis. Their benefits arise from the induction of the natural healing process with the release of various growth factors. The safest use of these various treatments is when the trauma or energy is the lowest, and cosmeceutics can augment the results. By combining these traumatic treatments with...
the chemical effects of vitamin A (normal maturation of cells), vitamin C, and antioxidants, one can expect

- healthier keratinocytes with faster healing of the epidermis;
- a thicker epidermis;
- better control of pigmentation and the prevention of postinflammatory hyperpigmentation;
- more intense collagen deposition from direct stimulation of the responsible genes;
- healthier collagen with topical vitamin C;
- thicker dermis with better support for blood vessels;
- healthier blood supply to facilitate healing and growth;
- greater elastin and collagen formation with added peptides, such as palmitoyl pentapeptide and palmitoyl hexapeptide.

SUMMARY

Cosmeceuticals have changed the world of skin care. It no longer makes sense to use simple plant extracts in skin care creams. The use of molecules derived from plants requires that they be highly refined and available in standard concentrations with scientifically proven effects. Cosmeceutical skin care is essential to minimize the ravages of the environment and may be used to complement facial cosmetic surgery and other operations that intend to rejuvenate skin anywhere on the body. By understanding the basics of the science of skin care cosmeceuticals, one can design cosmeceutical products that the end user can rely on to make smooth, fresh glowing skin that shows few signs of accumulated photodamage. Many doctors make the mistake of believing that they can achieve youthful skin by using AHAs, heavy peels, or other drastic techniques that destroy the epidermis measures such as laser resurfacing. The epidermis is far too important and complex to be destroyed or tortured into becoming smooth. For the first time in history, the general public has the chance to rehabilitate damaged skin at the same time as preventing photoaging. Healthy keratinocytes are ultimately responsible for a beautiful, resilient skin. The first aim of cosmeceutics must be to rehabilitate photoaged, inefficient keratinocytes and create a normal healthy epidermis that then sets up the possibility of improving the dermis.

Vitamin A, especially in its ester form, gives all the benefits of retinoic acid without the irritation. Its role is both preventative against photoaging as well as regenerative. Antioxidants work hand in hand with vitamin A and also complement sun protection but act only in preventing photoaging to a degree. Vitamin A may be considered as the agent that sets up a healthy skin and also organizes the “collagen factories,” but without vitamin C, healthy woven collagen will not be laid down. Because collagen deposition lies at the very heart of rejuvenating skin, vitamins A and C should always be used together. Iontophoresis and LFS enhance penetration of vitamins and active peptides and can help surgeons achieve realistic rejuvenation.

Numerous machines have been developed to try and build up the dermal collagen and elastin, but it has been repeatedly observed that rationally designed cosmeceuticals can achieve results similar to those seen from treatments using these machines. Cosmeceutical skin care is relatively inexpensive and will become more effective in controlling the environmentally induced skin damage.
REFERENCES


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