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# The Role of Cosmeceuticals in Antiaging Therapy

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## ABSTRACT

*As baby boomers get older, they have shown an increasing interest in maintaining a youthful appearance. As a result, there has been a corresponding increase in topical antiaging formulations, which are commonly referred to as cosmeceuticals. These products come with a seemingly limitless number of key active ingredients and claims of reducing the signs of aging and/or maintaining a youthful appearance. This paper reviews the more common cosmeceutical ingredients.*

**Key Words:** *Cosmeceuticals; alpha hydroxy acids; antioxidants; botanicals; exfoliants; depigmenting agents; moisturizers; retinoids; sunscreens*

As baby boomers begin to reach retirement age, there has been an increased interest in antiaging preparations, or cosmeceuticals, and their purported ability to enhance a person's more youthful appearance. Antiaging topicals, with their multiple claims, seemingly limitless key active ingredients, and complex formulations are leading the way in this huge growth industry of cosmeceuticals, especially as this segment of the population opts for less invasive, non-surgical alternatives to slow the effects of aging on the skin.

Market trends in the US for cosmeceuticals and antiaging products project sales of more than $16 billion by 2010.[1]

The term cosmeceutical was introduced by Albert

The term cosmeceutical was introduced by Albert Kligman in 1984 to refer to substances that exerted both cosmetic and therapeutic benefits.[2] Many contain biologically active ingredients, and in general, cosmeceuticals undergo tests to determine safety, but claims of efficacy are largely unsubstantiated.[3] Efforts have only recently been initiated to address the issues surrounding quality control and to establish industry standards and regulations. Demonstrating the skin effect of a cosmeceutical can be difficult; there are no placebos because anything that is applied to the skin will have an effect.

This term is not applied to the same products universally (e.g., sunscreen is considered to be an over-the-counter drug in North America, but a cosmeceutical in Europe), and the term "cosmeceutical" is not recognized by the US FDA. Categorization and regulation will depend upon how product claims are presented to the public.

## Vehicles

One of the most important parts of any cosmeceutical is the vehicle that carries the active ingredient into the skin.4 Vehicle delivery systems can:

- • augment the efficacy of the active ingredient
- • inactivate the active ingredient
- • improve the skin barrier
- • provoke allergic contact dermatitis.4

In some skin conditions, the vehicle may be as good as the active preparation, and it may take 3 months or more to see a difference.

## Cosmeceutical Research

There is limited research being done on cosmeceuticals in academic dermatology, and there have been no NIH grants available for cosmeceutical research to date. As a result, the best research comes from industry sponsored studies.

## Some Common Types of Cosmeceutical Ingredients

- Alpha Hydroxy Acids
- Antioxidants
- Botanicals
- Depigmenting Agents
- Exfoliants
- Moisturizers
- Peptides
- Retinoids
- Sunscreens
- Exfoliants

### Alpha Hydroxy Acids (AHAs)

Also referred to as fruit acids, they are a common ingredient found in cosmeceutical products. Examples include:

- Citric acid
- Glycolic acid
- Lactic acid
- Malic acid
- Pyruvic acid
- Tartaric acid

AHAs improve skin texture and reduce the signs of aging by promoting cell shedding in the outer layers of the epidermis and by restoring hydration. The mechanism of action is not completely understood. One hypothesis suggests that AHAs reduce the calcium ion concentration in the epidermis and, through chelation, remove the ions from the cell adhesions, which are thereby disrupted, resulting in desquamation. This is enhanced by cleavage of the endogenous stratum corneum chymotryptic enzyme on the cadherins, which are otherwise protected from proteolysis by conjugation with calcium ions. The resulting reduction of the calcium ion levels tends to promote cell growth and slow cell differentiation, thus giving rise to younger looking skin.[5]

### Antioxidants

Antioxidants reduce free-radical damage, thereby preventing impairment at the cellular level. They inhibit inflammation, which leads to collagen depletion, and they offer protection against photodamage and skin cancer.

However, there is no completely satisfactory agent available for humans. Explanations for this could include the fact that:

- Reactive oxygen species (ROS) affect different pathways in different situations and an antioxidant focused on 1 such pathway may be ineffective in a redundant pathway.
- ROS pharmacokinetics in the target tissue may not relate to that of the antioxidant.
- Bioavailability and target organ concentration of the antioxidant may be a limiting issue.[6]

Common antioxidants include alpha-lipoic acid (ALA), L-ascorbic acid (vitamin C), niacinamide (vitamin B3), N-acetyl-glucosamine (NAG), á-tocopherol, and ubiquinone (CoQ10).

**Alpha-lipoic Acid (ALA)**
Alpha-lipoic acid has anti-inflammatory properties and acts as an exfoliant. In a split face study, topical 5% ALA applied b.i.d. for 12 weeks reduced skin roughness, lentigines and fine wrinkles.[7] This agent does not protect against UV-induced erythema or reduce the number of sunburn cells.

**L-Ascorbic Acid (Vitamin C)**
There is clinical data to support the use of topical vitamin C to improve fine lines and reduce both pigmentation and inflammation,[8] and many cosmeceutical formulations contain this antioxidant. However, many of these formulations are not effective on the skin because:

- the concentration of L-ascorbic acid is too low.
- exposure of the product to air and light compromises the stability of the product.
- the L-ascorbic acid molecule (in the form of an ester or a mixture of isomers) cannot be absorbed or metabolized effectively by the skin.

In high enough concentrations (i.e., at least 10%) of the nonesterified, optimal isomer, this antioxidant does inhibit UV damage.9 It is important to note that stabilizing ascorbic acid presents many formulary challenges; however, a formulation that has an acid pH of approximately 3.[5] may optimize vitamin C absorption.[9] Newer formulations of stabilized ascorbic acid derivatives may prove to be more efficacious.

## Niacinamide (Vitamin B3)

Niacinamide is a potent antioxidant that is generally well tolerated. It improves the lipid barrier component of the epidermis, thus reducing transepidermal water loss, and acts as an inhibitor of melanosome transfer, resulting in reduced hyperpigmentation. Studies have revealed significant reduction in fine lines and wrinkles, hyperpigmented spots, red blotchiness, and skin sallowness, as well as improved skin elasticity.[10,11]

**N-Acetyl-Glucosamine (NAG)**
NAG is a more stable form of glucosamine, and may prevent new signs of photodamage from occurring, and fade existing imperfections by interrupting the chemical signals that promote melanin production. A placebo-controlled study comparing 3.5% NAG with the combination of 3.5% NAG plus 3.5% niacinamide on hyperpigmented spots showed a superior reduction in pigmentation in the combination treatment group vs. both the

superior reduction in pigmentation in the combination treatment group vs. both the placebo and NAG only groups. When combined they produced synergistic effects.[12]

**á-Tocopherol (Vitamin E)**
When taken orally, á-tocopherol protects membrane lipids from peroxidation. It has been shown to reduce sunburn cells after UV exposure, neutralize free radicals, and act as a humectant.13 Its activity can be renewed by combining it with a vitamin C preparation. As a component in topical formulations, it, like unmodified L-ascorbic acid, has shown some limited efficacy; however, when a stable formulation delivers a high concentration of the nonesterified, optimal isomer of this antioxidant, vitamin E does inhibit the acute UV damage of erythema, sunburn, and tanning, as well as chronic UV photoaging and skin cancer.9 Because vitamin C regenerates oxidized vitamin E, the combination in a cosmeceutical formulation is synergistic - particularly with regard to UV protection.[9]

**Ubiquinone (CoQ10)**
Ubiquinone is a naturally occurring, fat-soluble antioxidant and there is good in vitro evidence that it can suppress fibroblast production of UVA-induced collagenase, thereby reducing collagen breakdown.14 It has been shown to be effective against UVA mediated oxidative stress in human keratinocytes. Ubiquinone was also able to significantly suppress the expression of collagenase in human dermal fibroblasts following UVA irradiation.15 Another study showed that ubiquinone can strongly inhibit oxidative stress in the skin induced by UVB.[16] It is an effective antioxidant protecting the dermal matrix from both intrinsic and extrinsic aging.[14]

## Botanicals

Botanicals comprise the largest category of cosmeceutical additives found in the marketplace today. Their use is unregulated and often unsupported by science and their purported therapeutic properties remain largely unexplored.
Some botanicals that may benefit the skin include: green tea extract, ferulic acid, and grape seed extract.

**Green Tea Extract**
Research has shown that green tea (Cammelia sinensis) polyphenols are potent suppressors of carcinogenic activity from UV radiation and can exert broad protection against other UV-mediated responses, such as sunburn, immunosuppression, and photoaging.[17]

**Ferulic Acid**
This compound, which is derived from plants, is considered to be a potent antioxidant, and has been shown to provide photoprotection to skin.[17,18] Furthermore, when ferulic acid is combined with vitamins C and E, the product has been shown to provide substantial UV protection for human skin.19,20 Moreover, Murray et al. report that because its mechanism of action is different from sunscreens, ferulic acid could be expected to supplement the sun protection provided by sunscreens.[20]

**Grape Seed Extract**
This botanical has been established as a potent antioxidant and has been shown to speed wound contraction and closure.21 Topical application of grape seed extract has also been shown to enhance the sun protection factor in humans.[22]

## Depigmenting Agents

Skin-lightening agents added to product formulations have become increasingly popular. Common depigmenting ingredients include hydroquinone, ascorbic acid (vitamin C), kojic acid, and licorice extract (glabridin).

### Hydroquinone

Hydroquinone has been the agent of choice for skin lightening. However, there are concerns over exogenous ochronosis and permanent depigmentation, as well as possible carcinogenicity,[23] and it has been banned as an over-the-counter depigmenting agent in Europe, Australia and Japan.[24] The US FDA has proposed concentrations between 1.5% and 2% in skin lighteners.[25] A recent report suggested that this concern has been based mainly on studies with animal models utilizing long-term exposure at high dosages. Routine topical application may pose no greater risk than that from levels present in common foods.[26]

### Ascorbic acid (Vitamin C)

Ascorbic acid is a naturally occurring antioxidant found in citrus fruits and leafy green vegetables. It is hydrophilic, so skin penetration is low.

### Kojic acid

Kojic acid is a less commonly used bleaching agent. When combined with dipalmitate, there is improved skin penetration and greater stability, but there is little research to support its efficacy.[27]

### Licorice Extract (Glabridin)

Several studies on melasma have shown good efficacy with only mild irritation that disappeared with discontinuation.[25]

## Moisturizers

Moisturizers restore water content to the epidermis, and provide a soothing protective film. They improve the appearance and tactile properties of dry and aging skin, restore the normal barrier function of the skin, and reduce the release of inflammatory cytokines. Moisturizers comprise an important therapeutic component in the management of various skin conditions (e.g., eczema, psoriasis, pruritus, and aged skin)[29]

## Topical Peptides

Topical peptides are regarded as cellular messengers that are formed from amino acids and are designed to mimic peptide fragments with endogenous biologic activity. These pentapeptides (e.g., KTTKS) are comprised of a subfragment of type I collagen propeptide, and play a role in signalling fibroblasts to produce collagen in the skin,[30] which can improve the appearance of wrinkles.

One variation, the palmitoyl pentapeptide known as Pal-KKTKS (Matrixyl™, Sederma) was tested in a controlled, double-blind, left-right randomized, split-face study of 93 women between 35 and 55 years of age who had Fitzpatrick I-III type skin. Pal-KTTKS concentration was 3ppm; both groups were treated twice daily for 12 weeks. Improvements in wrinkle appearance and length were observed.[31]

## Retinoids

Retinoids are among the most common ingredients found in cosmeceuticals. In fact, they

are the most studied and have the most data behind them. They consist of natural and synthetic derivatives of vitamin A that reduce hyperpigmentation and inhibit enzymes from breaking down collagen. Many of their cosmeceutical claims are based on data derived from studies on tretinoin and other classes of retinoid drugs. Some key retinoids include retinoic acid (tretinoin), retinol, retinaldehyde.

**Retinoic Acid (Tretinoin)**

There is extensive literature on the use of tretinoin, which is considered to be one of the most potent compounds for treating the signs of aging and/or photodamaged skin, including fine lines, hyperpigmented spots, and wrinkles.[32-34] However, side-effects such as burning and scaling have limited its acceptance. In order to minimize these side-effects, various novel drug delivery systems are being developed.[34]

**Retinol (Vitamin A)**

Retinol is oxidized into retinaldehyde and then into retinoic acid, the biologically active form of vitamin A. In vivo studies showed that topical retinol had only a modest retinoid-like biologic activity compared with topical retinaldehyde and retinoic acid.[32] Two randomized, controlled trials reported significant improvement in fine wrinkles after 12 and 24 weeks of treatment, respectively.[35,36]

**Retinaldehyde**

Retinaldehyde is viewed in a large part as an intermediate form during the conversion of retinol to retinoic acid. Studies have shown that it does have activity in human skin.[33] Moreover, some studies have reported that this retinoid can produce significant clinical improvement in the appearance of fine and deep wrinkles.[32,37]

## Sunscreens

Sunscreens are the single most important cosmeceutical, because they protect skin against solar radiation, which is the most important damaging environmental agent. As a result, they help to prevent the signs of aging. To be effective, sunscreens should provide broad spectrum coverage that includes both UVA and UVB blocking agents to inhibit photoaging and be part of a daily skin care regimen. Sunscreens contain active ingredients that act as ultraviolet filters. The recommended application is 2mg/cm2, though this is rarely achieved in real-life practice.[38] Labeling changes proposed by the US FDA on sunscreen products are forthcoming.[39]

## Formulation Considerations and Conclusions

Although some product claims for the active ingredients used in cosmeceutical formulations are evidence-based, consumers often place their confidence in the claims made by the manufacturer. Without testing to assess the efficacy of key active ingredients in relation to overall product content, it is possible that at inadequate concentrations, any beneficial effect will become inapparent. Ensuring consistency of formulations is also an area that has been neglected and necessitates regulation.

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