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Revisiting the Skin Health and Beauty Pyramid: A Clinically Based Guide to Selecting Topical Skincare Products

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ABSTRACT

The original article "The Skin Health and Beauty Pyramid" was published in 2014. In the last 7 years, many new skin care innovations have been developed that were not available at the time of the first publication. New mechanisms of action for recently identified unmet skin aging needs along with novel ingredients have been commercialized that warrant the attention of dermatologists, skin care professionals, and patients. This article updates the original pyramid with these new concepts.

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INTRODUCTION

Pyramids are highly stable structures with a broad base and pointed thinner top that have stood thousands of years in harsh environmental conditions. Therefore, it is appropriate that the pyramid serve as an organizational model for the development of skin health and beauty treatment regimens. The original model was published in the *Journal of Drugs in Dermatology* in April 2014.[1] It was well received for its novel approach to cosmeceutical recommendations by dermatologists and skin care professionals and even resonated with patients for its simplicity. The original pyramid was designed to organize skin care into a hierarchy beginning with basic skin care issues affecting the stratum corneum, and then proceeding inward to epidermal and dermal considerations in an outside/inside approach.

The base of the pyramid was focused on protection and repair. Originally, protection from UVA/UVB radiation was considered along with the resulting DNA damage. Now, many more sources of external skin trauma beside solar radiation have been identified, including air pollution, digital pollution (blue light), burning tobacco, abnormal circadian rhythms, high temperature from infrared radiation, and alterations to the microbiome. The middle of the pyramid was focused on renewal, involving moisturization, exfoliation, and cell turn over. More sophisticated moisturizers are now possible due to the development of new cosmetic ingredients, such as hyaluronic acid, synthetically produced on the human model of dermal glycosaminoglycans. Finally, the top of the pyramid focused on dermal stimulation with activation and regeneration induced by peptides and growth factors, but we can now also add stem cells to the list of available technologies.

This updated skin health and beauty pyramid includes newer introductions since 2014 to present the physician, skin care professionals, and patients with a current organized hierarchical approach to healthy skin.

Pyramid Base: Protection and Repair

The basis for any skin care regimen must be sun protection in the form of sunscreen. Sunscreens are considered over-the-counter (OTC) drugs in the United States and as such new sunscreen ingredients must be approved by the FDA. No new sunscreen active ingredients have been approved since 2014, yet technology has improved with less greasy, sticky vehicles that are more consumer acceptable. While the consumer may apply more sunscreen more frequently due to better aesthetics, sunscreen technology in terms of better ingredients for photoprotection has come to a standstill. Yet, sunscreens that protect against UVA and UVB radiation are only part of the story. It is now widely recognized that near infrared (IRA; 760–1400 nm), visible light (400–760 nm), and blue light can induce skin damage.

Visible light accounts for 40–45% of the electromagnetic radiation reaching the skin from the sun inducing the formation of reactive oxygen species and promoting photoaging. Visible light causes pigment darkening in Fitzpatrick skin types IV–VI more rapidly than UVA radiation possibly accounting for challenges in treating melasma and post-inflammatory hyperpigmentation in this population. The inorganic sunscreens that are optically opaque filters, such as zinc oxide and titanium dioxide, can reflect and scatter visible light when used in non-nano forms. These sunscreen ingredients should be included in products selected for antiaging purposes, especially in higher

Fitzpatrick skin type patients. A botanical extract, Fernblock®, obtained from the tropical plant *Polypodium leucotomos*, is a potent antioxidant and has shown to protect against damaged induced by visible light. Taken orally, Fernblock has shown to be effective in reducing visible light induced pigmentation.[2] Regarding infrared light, 50% of the electromagnetic energy reaching the earth is infrared with infrared A (IRA) accounting for about one third of the electromagnetic energy. Infrared can penetrate the skin producing an increase in skin temperature and activating mitochondrial reactive oxygen species (ROS) via up-regulation of MMP-1, MMP-3, and MMP-13. This results in collagen destruction accounting for the coarse wrinkling seen in human skin exposed to repeated high temperature. There are generally few active ingredients that shield against IRA although some antioxidants have been demonstrated orally and/or topically to help protect against IRA-induced ROS production and MMP-1 expression.

A new form of light injury, known as digital light pollution or high energy visible light damage, is blue light (412–426 nm) at high fluence.[3] Porphyrin-containing enzymes and flavoproteins are thought to be the photoreceptors for blue light damaging the mitochondrial respiratory chain. Computer screens, cell phones, and other digital devices produce this light. Opaque blocking agents, such as pigments, charcoal, red algae, and the *Polypodium leucotomos* extract before mentioned, are being incorporated into skin care products to prevent the blue light from reaching and damaging the skin. In addition to electromagnetic radiation impacting the skin, pollutants found in the air can also generate ROS and prematurely age the skin. Most of the damaging pollution contains nanoparticles generated by combustion. This includes the smoking of tobacco products where the burning of the plant material creates highly energetic nanoparticles that damage the skin. Air pollution from internal combustion engines or factory exhaust also contains nanoparticles that damage the skin. One method to minimize skin damage from aerosolized nanoparticles is to prevent them from touching the skin, which can be achieved by wearing a sunscreen, moisturizer, or facial foundation. Pollutants can also damage skin by activating Aryl hydrocarbon receptors (AhR), which trigger hyperpigmentation, MMP-1 expression, and damage to keratinocytes. Inhibition of the activation of AhR by ingredients such as the extract of *Deschampsia antarctica* has been shown to protect against morphological alterations to skin structure and prevent DNA damage induced by pollutants in a human skin model. It also helps to enhance the skin barrier function by increasing the production of loricrin.[4,5] *Deschampsia antarctica* is an extremophile plant that grows in the Antarctic in an environment characterized by very low temperatures, high oxygen concentrations, high salinity, and intense solar radiation.

Another approach to minimizing problems associated with ROS induced skin damage is the use of topical and/or oral antioxidants. Antioxidants must be considered inactive ingredients, as they are not listed on the sunscreen monograph and cannot be claimed as photoprotectors. Antioxidants are incorporated into some sunscreens because of their ability to scavenge and reduce ROS levels and may suppress ROS formation by 2.4-fold in SPF 15 formulations. Ingredients that are used for this purpose include retinol, ascorbic acid, alpha-tocopherol, and green tea polyphenols, among others, but they must be stabilized in formulation, so they do not undergo oxidation.[6] Prevention of DNA damage from ROS is minimized, but not eliminated, through the use of sunscreens and antioxidants. Another functional target for cosmeceuticals is DNA repair. Nicotinamide (amide form of vitamin B3) prevents the UV-induced ATP depletion boosting cellular energy and enhances DNA repair activity.[7] Fernblock has been demonstrated to induce and accelerate repair of DNA damage, by reducing and preventing the formation of cyclobutane pyrimidine dimers (CPD) and 8-oxo-dGuanine caused by UV exposure.[8] DNA repair enzymes, such as endonucleases, glycosylases, and photolyases, have been developed.[9] The T4 endonuclease V recognizes CPD and repairs DNA by catalyzing glycosylase to release thymine and then uses AP lyase to incise the phosphodiester backbone at the site of the missing base to cause a single-stranded break. The cell then supplies exonuclease to remove the base and then polymerase fills the gap thus repairing the DNA. Photolyases are not found in mammalian cells but are used for DNA repair in bacteria and plants. This mechanism uses blue light to repair DNA by catalyzing a reaction that transfers electrons which split the cyclobutane ring in the damaged DNA.[10] DNA repair enzymes can be delivered to the skin in liposomes with a diameter of about 150 nm.

Another new concept in protection and repair is the composition of the microbiome, the bacterial flora that covers the entire skin surface representing the collective genome of the indigenous microorganisms colonizing the whole body.[11] While the "normal" microbiome has not been confirmed, it is known that it varies by sex, age, body location, and immune status. UV radiation can induce skin microbiome alteration.[12] Skin care products have been developed based on prebiotic, probiotic, and postbiotic principles. Prebiotic skin care contains ingredients that are able to encourage the growth of microbiome organisms while probiotic skin care contains either live bacteria, requiring refrigeration of the product, or ultrasound-inactivated bacterial extracts. Postbiotic products contain non-viable bacterial products or metabolic by-products from postbiotic bacteria, such as enzymes, peptides, peptidoglycan-derived muropeptides, polysaccharides, cell surface proteins, etc. Some skin care companies are now testing their formulations to ensure they do not cause microbiome damage making the claim "microbiome friendly" or "microbiome neutral." However, more research is needed in the area of microbiome protection.

Pyramid Middle: Renewal
(Moisturization, Exfoliation, and Cell Turnover)

The next layer of the skin pyramid is the middle and encompasses moisturization, exfoliation, and cell turnover. Here we have moved beyond the stratum corneum and viable epidermis into the epidermis and superficial dermis. Moisturization is the basis of the pyramid middle, since the basic mechanism of action for many cosmeceuticals is to enhance skin water content thereby reducing fine lines of dehydration. While moisturizing ingredients are typically the basis for the vehicle in most cosmeceutical products, the vehicle here is an important active. Moisturizers function by decreasing transepidermal water loss (TEWL) by placing a water-resistant coating over the skin surface. This can be accomplished with occlusive agents, such as petrolatum, lanolin, shea butter, waxes, silicones, mineral oil, vegetable oils, etc. Reducing TEWL creates an environment for barrier repair allowing the skin to restore natural water balance; however, in low humidity conditions under 40%, water will continue to be lost to the environment. Thus, moisturizers must also contain humectants that draw water from the dermis to the epidermis and possibly from the environment, but the humidity must exceed 70%. Humectants draw water, but the skin barrier must retain the water, otherwise TEWL will increase and accelerate skin dehydration.

The water content in the skin is assessed by a technique known as corneometry. Here a capacitive sensor is used to measure the permittivity of upper skin layers, which correlates with skin hydration. Substances that can increase skin water measurements act like sponges and mimic the natural humectants in the dermis, which are glycosaminoglycans. The most widely recognized glycosaminoglycan is hyaluronic acid, originally cross-linked and developed as an injectable facial filler, but now synthetically available in topical cosmeceuticals. Other humectants include sodium PCA, glycerin, sorbitol, urea, sodium lactate, propylene glycol, butylene glycol, honey, etc. Well-formulated cosmeceutical moisturizers include both occlusive and humectant ingredients to combine both mechanisms of remoisturization. In summary, the goals of a moisturizer are: 1) to increase skin hydration, 2) to make the skin feel smooth and soft, 3) to deliver cosmeceutical actives to the skin, and 4) to improve skin appearance.

Rough scaly skin can possess an excellent skin barrier with adequate water content, but still appear dry and unattractive. This may be due to a desquamatory failure. The enzymes that provide for skin exfoliation require a moist environment for activity, thus moisturization may also encourage desquamation; however, desquamation can be enhanced by the topical application of alpha hydroxy acids (AHAs). AHAs are a group of organic carboxylic acids distinguished by a substituted hydroxy group covalently bonded to the α-carbon of a carboxylic acid.[13] AHAs, such as glycolic acid, lactic acid, and malic acid, can disrupt the ionic bonding at the level of the stratum granulosum allowing the skin cells to slough.[14,15] The epidermal effects of AHAs are a thinned stratum corneum with epidermal acanthosis and decreased melanogenesis while the dermal effects of AHAs are increased synthesis of glycosaminoglycans and increased dermal thickness.[16,17]

This is in contrast to salicylic acid, a lipophilic acid also used for effective exfoliation in the oily areas of the face and in the sebum laden pores. Salicylic acid appears to eliminate the stratum corneum layer by layer from the outermost level downward.[18] This is in contrast to AHAs, which appear to diminish cellular cohesion between the corneocytes at the lowest levels of the stratum corneum.[19] This difference is probably due to the water-soluble characteristics of the AHAs, which readily penetrate into the stratum corneum, and the oil-soluble characteristics of salicylic acid, which remains on the stratum corneum. Exfoliation, in combination with moisturization, is extremely effective in smoothing the skin surface and improving skin texture, which patients notice as increased radiance and luminosity. Too much aggressive exfoliation can damage the skin barrier and decrease water content, thus the two activities must balance one another.

Retinoids represent another important cosmeceutical ingredient category capable of producing receptor specific effects including regulating growth of epidermal cells and promoting differentiation of cell lines.[20] The retinoid family includes retinol, retinyl esters, retinoic acid, retinyl palmitate, and retinsphere technology. Retinyl palmitate is the most stable of the vitamin A esters, however it is not very biologically active. Cosmeceutical activity of retinyl palmitate is thought to occur by cutaneous enzymatic cleavage of the ester bond and subsequent conversion of retinol to retinoic acid. Retinol, another common cosmeceutical retinoid is more readily converted to retinoic acid, but only small amounts of retinol can be converted by the skin.[21] Retinsphere is the combination of two retinoids: a retinoic acid ester, hydroxypinacolone retinoate, and retinol in glycospheres or microsponges. This combination offers more chemical stability and improves retinol efficacy. Treatment tolerance with this combination is very high and does not cause the irritation often observed with other retinoids.[22-24]

Pyramid Top: Activation and Regeneration

We have now arrived at the top of the pyramid, which is characterized by dermal benefits to include dermal activation and regeneration. A variety of new cosmeceutical technologies have attempted to optimize skin from the inside including peptides, growth factors, stem cells, and circadian rhythm modifiers.

Peptides form the building blocks for proteins and are composed of amino acids, usually representing fragments of biologically active proteins. Peptides can be added to topical formulations to allow receptor modulation, activate enzyme release, or regulate protein production. The 3 families of peptides currently marketed

include carrier peptides, signal peptides, and neurotransmitter peptides.[25] Carrier peptides are designed to bind to another ingredient and facilitate transportation of the agent to the active site.[26] An example of a carrier peptide is GHK-Cu (Glycyl-L-histidyl-L-lysine Copper), which was designed to deliver copper, a trace element necessary for healing, into wounds.[27] This peptide, composed of glycine, histidyl, and lysine, was isolated from human plasma and then synthetically engineered for use in cosmeceuticals designed to minimize the appearance of fine lines and wrinkles in conjunction with the moisturizing vehicle. Signal peptides are intended to increase collagen, elastin, fibronectin, proteoglycan, and glycosaminoglycan production.[28] The most popular signal peptide is palmitoyl pentapeptide, abbreviated Pal-KTTKS, composed of lysine, threonine, threonine, lysine, and serine. It is a procollagen I fragment that demonstrated in vitro to stimulate the production of collagen I, III, and IV.[29] Procollagen I fragments are intended to act as a signal down-regulating the production of collagenase. Other signal peptides include the hexapeptide VGVAPG, composed of valine, glycine, valine, alanine, proline, and glycine, which is thought to attach to receptors in the membrane of the fibroblast stimulating the synthesis of collagen, but decreasing the synthesis of elastin.[30] Neurotransmitter peptides are intended to inhibit the release of acetylcholine at the neuromuscular junction and mimic botulinum toxin by selectively modulating SNAP-25. Acetyl hexapeptide-3 mimics the N-terminal end of the SNAP-25 protein inhibiting SNARE complex formation, thereby inducing muscle relaxation and minimization of wrinkles.[31]

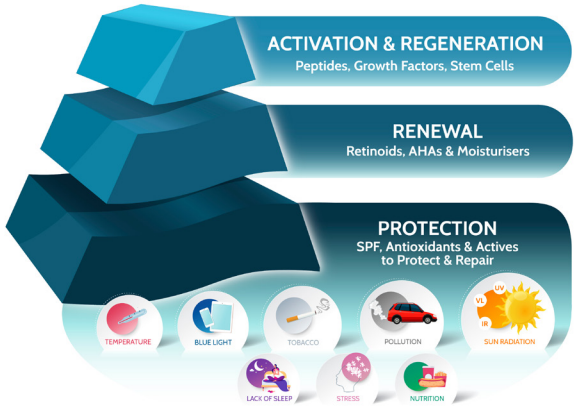
Another mechanism for inducing activation and regeneration is the use of growth factors (GFs) and cytokines. The most commonly used growth factors in cosmeceuticals are transforming growth factor β1 (TGF-β1) inducing keratinocyte migration, epidermal growth factor (EGF) inducing epidermal proliferation, platelet derived growth factor (PDGF) inducing macrophage activation and matrix production, and fibroblast growth factor (FGF) such as the activity of the secretion of *Cryptomphalus aspersa* (SCA), which induces fibroblast proliferation and migration showing skin regenerative properties.[32] The challenge with topical applied growth factors is their large molecular weight inhibiting skin penetration. Hydrophilic molecules larger than 500 daltons have very low skin penetration and thus remain inactive on the skin surface. Growth factors typically are in the range of 15,000 daltons and thus they must be penetration enhanced for skin delivery.[33] Also, it seems that a small fraction of topically applied GFs penetrating into superficial epidermis, can elicit a fibroblast-mediated response in the dermis and signaling molecules may pass through skin structures.[34]

Dermal stimulation can also be achieved through the use of stem cells, either of plant or animal origin, which are pluripotential cells capable of indefinite propagation in an undifferentiated state. Stem cells are present in the skin in the bulge region of the hair follicle, the interfollicular epidermis, and the sebaceous gland. Live stem cells cannot survive in a cosmeceutical at room temperature in a preservative laden formulation, thus ingredients that are stem derivatives are incorporated skin care products. An example of such an ingredient is *Crytomphalus aspersa* snail egg extract. This ingredient in vitro improved stem cell migration and differentiation, promoted extracellular matrix formation, improved cell adhesion, and stimulated the migration of epidermal keratinocytes and dermal fibroblasts.[35]

The last major concept in activation and regeneration is the modulation of circadian rhythms, based on fluctuations related to the day/night cycle, hormones, meals, sleep/wake cycle, adrenal gland production, thyroid gland, and clock genes.[36] The human circadian clock is in the suprachiasmatic nucleus, located in the hypothalamus, with information transmitted via the retina that contains specialized photosensitive ganglion cells. Circadian rhythms are important in keratinocytes, fibroblasts, melanocytes, mast cells, and hair follicles.[37] Skin functions affected by circadian rhythms include free radical production and neutralization, DNA damage and repair, keratinocyte/fibroblast differentiation and proliferation, and barrier and immune functioning.[38] During the day, the skin has the highest pH, sebum production, and thickness with the lowest cell proliferation. However, at night, the skin has the highest DNA repair, cell proliferation, barrier permeability, skin penetration, and blood flow. This has led to a new concept in skin care based

FIGURE 1. Skin Health and Beauty Pyramid.

FIGURE 2. Skin Health and Beauty Pyramid with environmental and lifestyle aggressors.



on optimizing products to address the diurnal variation in skin needs.[39] The Skin Health and Beauty Pyramid, and the Skin Health and Beauty Pyramid with environmental and lifestyle aggressors, are shown in Figure 1 and Figure 2, respectively.

CONCLUSION

The skin pyramid remains a useful concept for the organization of cosmeceutical skin care. All three levels of the pyramid must be addressed for optimal skin rejuvenation from the outer to the inner skin layers. This includes the pyramid base representing protection and repair, the middle of the pyramid representing renewal with moisturization, exfoliation, and cell turnover, and the top of the pyramid representing activation and skin regeneration. This update of the 2014 original skin pyramid includes many new discoveries in skin physiology that are translating into ingredient driven technologies in the current cosmeceutical market.

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