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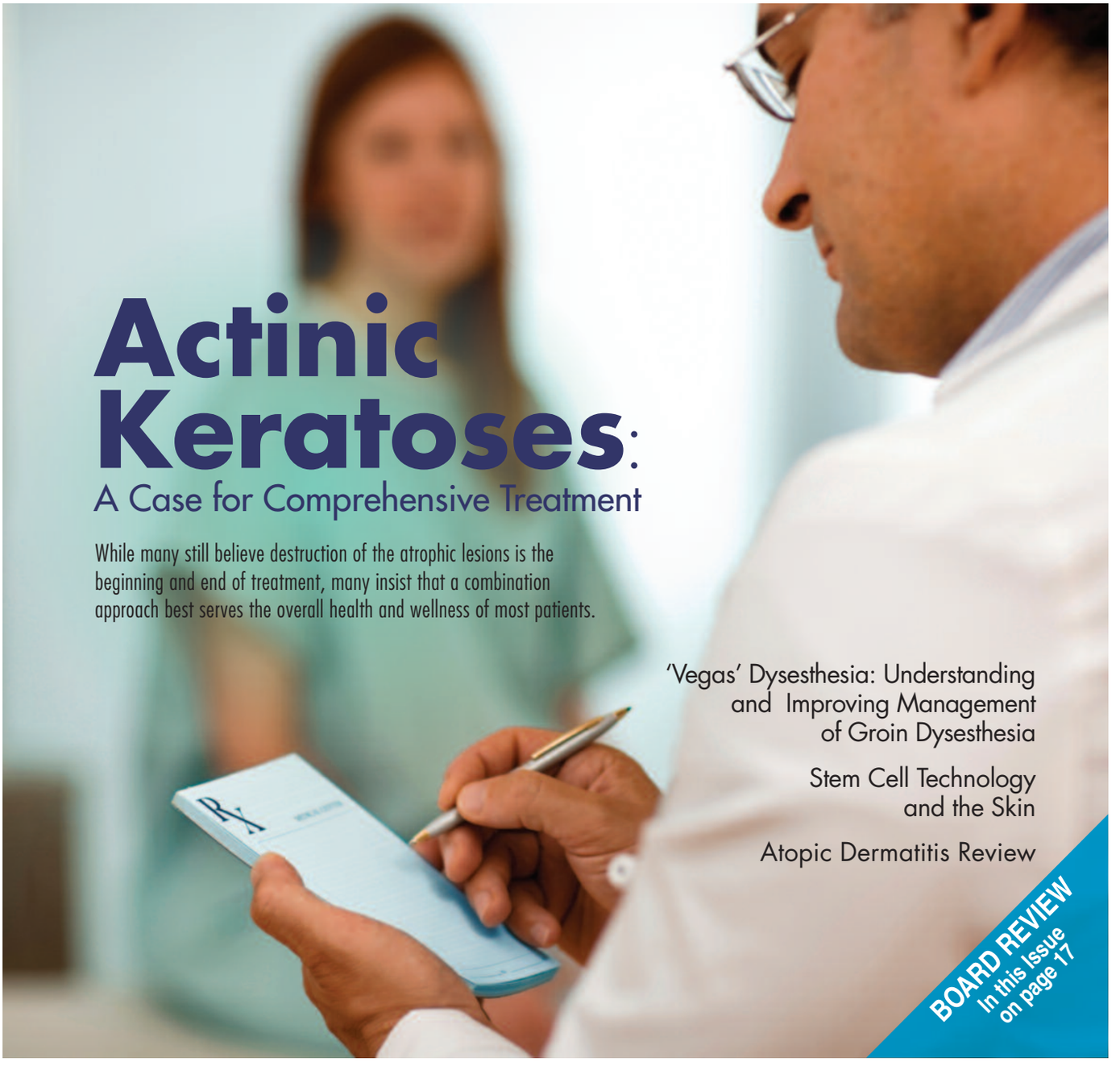
PRACTICAL AND CLINICAL ISSUES FOR TODAY'S DERMATOLOGIST



Actinic Keratoses: A Case for Comprehensive Treatment

While many still believe destruction of the atrophic lesions is the beginning and end of treatment, many insist that a combination approach best serves the overall health and wellness of most patients.

'Vegas' Dysesthesia: Understanding and Improving Management of Groin Dysesthesia

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Stem Cell Technology and the Skin

A look at the current research on plant-derived stem cell extracts and their potential role in cosmeceutical and skin care products.

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The ability to replace, instead of simply repairing, damaged skin cells is becoming more of a possibility with the advancements in plant stem cell technology. Scientific research supports the use of certain plant stem cell extracts, but further research may be needed to support the efficacy of others. At this time, much of the research focuses on the photoprotective properties of dietary botanicals, citing the potential of topical products that use plant extracts with the same characteristics. Keeping abreast of plant-derived stem cell research as it evolves is essential for making optimal treatment choices as plant stem cell technology is incorporated into anti-aging skin care.

SKIN STEM CELLS

Before considering the addition of stem cells into cosmeceuticals, it is critical to understand the role of stem cells in the skin. The majority of skin stem cells reside in the basal layer of the epidermis. Their primary function is to replenish the skin as it undergoes normal homeostatis and wound repair.[1] Like all stem cells, those in the epidermis are undifferentiated and capable of dividing themselves for extended periods of time and differentiating into multiple lineages based on their tissue origin.[1,2] When a stem cell divides, the daughter cells have the potential to either remain a stem cell, like the parent cell, or they can differentiate into cells with a more specialized function known as progenitor cells.

After these progenies experience several rapid divisions in the basal layer, they cease dividing and travel through the suprabasal layers to the tissue surface. Once there, they progressively differentiate, switching from expression of one set of keratins to another. Eventually their nuclei degenerate, producing an outer layer of dead keratinized cells that are shed. Stem cells continuously renew the epidermis, with a turnover time of approximately 1 month.[2]

Epidermal stem cells also are stored in a microenvironment called the bulge, which is located at the base of the hair follicle. They remain dormant there until recruited by neighboring cells to help repair the skin. The stem cell's characteristics are determined by the epigenetic signal it receives.

The existence of several distinct, highly compartmentalized stem cell populations have been reported in the literature.[3,4] The data suggests that the loss of a stem cell in one structural unit is quickly replaced by stem cells in the adjacent unit, which demonstrates the multipotential nature and developmental flexibility of skin cells.[5]

SKIN CELL DAMAGE

Although the skin constantly renews itself throughout an adult's lifetime, these long-term self-renewing stem cells begin to regenerate more slowly as part of the aging process. It is believed that the impaired wound healing rate in aging skin may be due either to impaired stem cell mobilization or a reduced number of stem cells able to respond to proliferative signals.[3] Lost or dying cells begin to outnumber their regenerated counterparts, which likely leads to common signs of aging, such as rhytids and laxity. It is for this reason that stem cells make intriguing additions to anti-aging products.

Additionally, ultraviolet (UV) radiation causes damage to the skin, including photoaging, inflammation, erythema, sunburn and cancers.[6-9] Photoaging is characterized by wrinkles, altered pigmentation and loss of skin tone. Specifically, ultraviolet A (UVA)

and ultraviolet B (UVB) radiation have been proven to produce DNA damage directly and indirectly through oxidative stress.[10] Solar radiation induces the generation of reactive oxygen species (ROS), which interact with proteins, lipids and DNA, altering cellular functions. Although the epidermis is composed primarily of keratinocytes that are rich in ROS detoxifying enzymes, an increased generation of ROS can overwhelm the skin's natural defenses.

Furthermore, ROS have been shown to mediate the phosphorylatin of protein kinases through a series of cascades, such as mitogen-activated protein kinases (MAPK), and activate transcription factors, such as nuclear factor-KB (NF-*k*B) and activator protein 1 (AP-1). These activities may contribute to cell proliferation, apoptotic cell death, inflammation and cancer.[10,11] The upregulatation of gene expression through intracellular signal transduction pathways likely contributes to the development of skin cancer at the tumor promotion stage.[10] Since this stage is reversible, it is a prime target for preventing, reversing or slowing the process. Stem cells have been proven to be protective against UV-induced radiation and ROS through a variety of mechanisms. It is this protective quality that also makes them useful for daily use in skin care.

PLANT STEM CELLS BENEFIT HUMAN SKIN

In recent years, researchers have identified naturally occurring botanicals with substantial antioxidant activity proven to protect skin stem cells from UV-induced oxidative stress, inhibit inflammation, neutralize free radicals and reverse the effects of photoaging. Consequently, cosmeceutical products containing extracts derived from plant stem cells have the ability to promote healthy cell proliferation and protect against UV-induced cellular damage in humans.

In contrast to epidermal stem cells, plant stem cells are totipotent, meaning they are capable of regenerating an entirely new, whole plant. Through innovative plant stem cell technology, scientists are able to extract tissue from botanicals. Thus, the plant's ability to regenerate stem cells can be harnessed for use in humans.

The use of stem cells derived from botanicals, rather than human stem cells, avoids the controversy surrounding the source or methods of extraction of human stem cells while still harnessing the potential of these intriguing cells.

RESEARCH SUPPORTS PLANT STEM CELL EXTRACTS

There are several plant-derived stem cell extracts available for cosmeceutical use; however, research has predominately focused on three with various levels of scientific rigor. Components found in grape, lilac and Swiss apple have been shown to be rich sources of phyto stem cells. Probably the most widely and longest studied botanical is the *vitis vinifera*, otherwise known as the grape seed. Studies dating back more than a decade suggest that grape seeds are known to contain anti-inflammatory properties, prevent skin aging, scavenge oxygen free radicals and inhibit UV radiation-induced activity.[12] More recently published *in vitro* and *in vivo* studies have identified proanthocyanidins — a group of polyphenolic bioflavonoids — in grape seeds and their stem cells as being responsible for its high anti-tumor-promoting activity because of their strong antioxidant effect.[11-17]

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The mechanism of action is not entirely understood, but it appears that the photoprotective effects of grape seed proanthocyanidins (GSPs) are mediated, at least, through protection of the endogenous antioxidant defense system and prevention of photodamage of macromolecules, lipids, proteins and DNA, which leads to inhibition of activation of the MAPK and NF-*k*B pathways.[11,16] Some studies have demonstrated that GSPs exert a significantly stronger oxygen free radical scavenging effect than vitamins C and E.[18,19] When topically applied, GSPs have demonstrated substantial photoprotective effects. As an example, when a gel formation containing Jacquez grapes was topically applied to healthy human volunteers, it afforded significant *in vivo* protection against UVB light-induced skin erythema.[20]

Like grape seed, verbascoside extracted from various plants, including the *syringa vulgaris* or common lilac, is known to have antioxidant properties.[21,22] When studied *in vitro* and *in vivo*, verbascoside was found to possess significantly accelerated wound healing and remarkable anti-inflammatory action.[23] These effects were attributed to its ability to inhibit the ROS release by recruiting pro-inflammatory cells to the damaged skin. In fact, the verbascoside-containing extracts were found to be more effective than both hydrocortisone and triamcinolone in inhibiting inflammation.[23]

Although verbascoside is known to rapidly repair DNA oxidative damage, its mechanism of action is not clearly understood. In one study, verbascoside dramatically impaired NF-*k*B and AP-1 binding activity, suggesting that it has distinct mechanisms in the suppression of oxidative stress induced in keratinocytes by different stimuli.[24] Thus, verbascoside may offer protection of the skin from both inflammatory and environmental insults. However, other studies attribute verbascoside's ability to quickly repair DNA damage to its non-enzymatic fast repair mechanisms and not to its scavenging activity for ROS.[25-27] Its fast repair reaction has the added benefit of preventing the ROS from causing further damage.

While other plant stem cell extracts are currently being used in topical products, further research should be done to prove the efficacy. An ingredient manufacturer's study showed that a 0.1% concentration of stem cells extracted from Swiss apple stimulated the proliferation of human stem cells by 80%.[28] In a trial with 20 patients, a cream containing the apple extract was found to reduce wrinkle depth by 8% after 2 weeks and 15% after 4 weeks. Similarly, a cream and serum containing stem cells extracted from the edelweiss plant, which has been investigated for its anti-inflammatory properties, is reported to reduce wrinkle depth.

Additional research is needed to verify the validity of these studies.

EXTRACTS CAN ENHANCE TOPICAL PRODUCTS

Currently, much of the scientific research focuses on the use of dietary botanicals. However, many researchers acknowledge the potential benefits of their use in sunscreens, skin care topicals and moisturizing creams.

The key to developing effective cosmeceutical products is recognizing that the various plants have different properties as well as different mechanisms of action. Thus, products should be formulated to target the specific botanical's effects.

As an example, both grape seed and verbascoside have been proven to protect skin from UV oxidative stress. Although sunscreens are incredibly valuable, their inability to completely prevent UV-induced skin cancer — due to inadequate patient use and incomplete spectral protection — demonstrates the need for additional chemopreventive methods.[29] Using sunscreens in conjunction with phyto stem cell-rich ingredients harnesses the photoprotective properties of these plants, which may be useful in providing additional prevention against UV-induced skin damage and other skin disorders caused by UV radiation.[17,29] For example, components of grape stem cell extract have been shown to absorb radiation from the entire UVB spectrum and part of the UVA spectrum, and when applied topically they can provide additional protection against radiation penetration.[28]

Additionally, these stem cell-rich botanicals are known to inhibit inflammation and combat destructive free radical injury that leads to photoaging. Combining stem cell extracts from grape and lilac leaf with other anti-aging ingredients, such as neuropeptides, L-ascorbic acid (vitamin C) and alpha hydroxy acids, can yield an ideal combination that can work synergistically to treat and protect the skin.

As the scientific support for plant-derived stem cell research continues to grow, it is important to understand what these botanicals offer and how they work. In doing so, plant stem cell extracts scientifically proven to work can be incorporated into cosmeceutical products that hold the promise of not only stimulating the proliferation of human skin stem cells, but also protecting the skin from UV-induced oxidative damage.n

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Disclosures: Dr. Linder is Chief Scientific Officer, PCA SKIN, is National Instructor, Dermik Aesthetics (Sculptra), and National Instructor, Allergan Facial Aesthetics.

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