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Review

Active ingredients against human epidermal aging

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ABSTRACT

The decisive role of the epidermis in maintaining body homeostasis prompted studies to evaluate the changes in epidermal structure and functionality over the lifetime. This development, along with the identification of molecular mechanisms of epidermal signaling, maintenance, and differentiation, points to a need for new therapeutic alternatives to treat and prevent skin aging. In addition to recovering age- and sun-compromised functions, proper treatment of the epidermis has important esthetic implications. This study reviews active ingredients capable of counteracting symptoms of epidermal aging, organized according to the regulation of specific age-affected epidermal functions: (1) several compounds, other than retinoids and derivatives, act on the proliferation and differentiation of keratinocytes, supporting the protective barrier against mechanical and chemical insults; (2) natural lipidic compounds, as well as glycerol and urea, are described as agents for maintaining water-ion balance; (3) regulation of immunological pathogen defense can be reinforced by natural extracts and compounds, such as resveratrol; and (4) antioxidant exogenous sources enriched with flavonoids and vitamin C, for example, improve solar radiation protection and epidermal antioxidant activity. The main objective is to provide a functional classification of active ingredients as regulatory elements of epidermal homeostasis, with potential cosmetic and/or dermatological applications.

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1. Introduction

Epidermis, the most exposed skin part, directly contacts the external environment. It is assembled by multiple superposed cell layers that form an effective protection barrier (Baroni et al., 2012; Madison, 2003). As a complex system, which also captures environmental stimuli, epidermis is composed of several cell types such as keratinocytes, melanocytes, Langerhans cells, and Merkel cells (Boulais and Misery, 2008). Keratinocytes are the most abundant cell type constituting 80–95% of epidermal cells (Brohem et al., 2011; Ulmann et al., 2007).

Due to constant desquamation, epidermis needs continuous renewal, which begins with multiplication of proliferative cells

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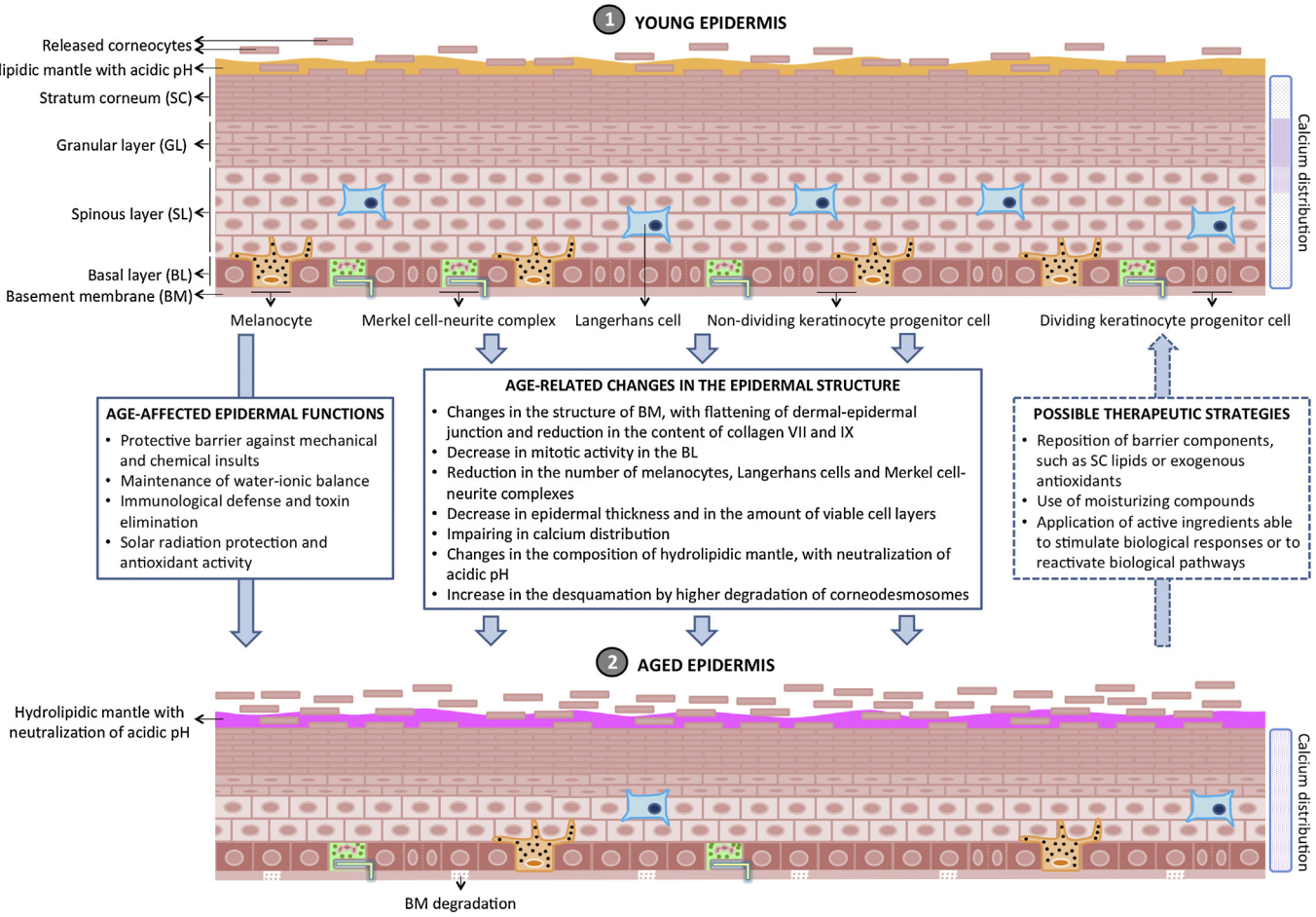

Fig. 1. Molecular, cell and morphological changes associated with epidermal aging. As the epidermis ages, it undergoes a series of structural modifications (Bergman et al., 2000; Choi et al., 2007; Chu and Kollias, 2011; Denda et al., 2003; Hachem et al., 2005; Levakov et al., 2012; Scharffetter-Kochanek et al., 2000; Zouboulis and Makrantonaki, 2011) that directly impact its physiological functions, compromising the natural protective barrier of the organism. Diagram indicating calcium distribution points to a higher ion concentration in the granular layer (GL), darker colored, region in young epidermis (1). In older epidermis (2) calcium gradient is lost and calcium is possibly distributed homogeneously among the skin layers. Possible therapeutic alternatives are different forms of action of active ingredients or compounds capable of helping to recover age-affected physiological functions to an extent that will approximate them as nearly as possible to those in young epidermis.

in the innermost layer, generating keratinocytes that undergo differentiation as they are driven outwards with cell divisions (Fuchs and Raghavan, 2002; Milstone, 2004). Keratinocyte differentiation is marked by molecular, structural, and functional changes, resulting in a stratified epidermis in which the different strata, arranged from the inner to the outer surface, constitute the basal layer (BL), spinous layer (SL), granular layer (GL), and stratum corneum (SC), respectively (Fuchs and Raghavan, 2002; Simpson et al., 2011). The palms and soles possess an additional layer – stratum lucidum (SL) – between GL and SC (Brohem et al., 2011). In SC, keratinocytes reach their highest level of differentiation and are then known as corneocytes – dead, enucleated, and morphologically flat cells composed of protein and lipid blocks bonded to one another and immersed in a lipid matrix (Eckhart et al., 2013).

More than just a barrier for mechanical protection, epidermis is a metabolically active tissue in constant dynamic balance and periodically undergoes complete renewal cycles (Fuchs and Raghavan, 2002). The working of the epidermis seems paradoxical, since it is highly stable in protecting the organism from external aggression and, at the same time, allows its cell components the required flexibility to ensure tissue renewal and capability of response to different stimuli (Simpson et al., 2011). This ability makes the epidermis a decisive component for maintaining body homeostasis. Over the years, however, epidermal primary functions may gradually falter (Elias and Ghadially, 2002). Physiological wear from skin aging is a consequence of damage that accumulates throughout the organism's life and is caused both by intrinsic factors (physiological components and genetic predisposition) and extrinsic factors (external insults, particularly from solar radiation) (El-Domyati et al., 2002; Farage et al., 2008a). Molecular, cell-related, and morphological changes in aged epidermis not only compromise its protective role, but also contribute to the appearance of skin symptoms, including excessive dryness and pruritus (White-Chu and Reddy, 2011), as well as increased predisposition to formation or deepening wrinkles (Kuwazuru et al., 2012), dyspigmentation (Longo et al., 2013), fragility and difficulty to heal injuries (Bourguignon et al., 2013; Calleja-Agius et al., 2007), alteration in skin permeability to drugs (Bourguignon et al., 2013), impaired ability to sense and respond to mechanical stimuli (Wu et al., 2011), skin irritation (Bourguignon et al., 2013), and tumor incidence (Farage et al., 2008b; Wolf et al., 2013) (Fig. 1).

Skin aging involves systemic changes as well as changes in the entire skin (Waller and Maibach, 2006, 2005; for details, refer to Farage et al., 2010). Although most investigations still concern dermis, mainly because of its abundant content in extracellular matrix (ECM), recent studies have targeted epidermal aging and possible therapeutic options. In addition to their health-related implications, epidermal alterations can lead to changes in appearance or image that may have a high esthetic and psychosocial impact (Jiang and DeLaCruz, 2011). Moreover, search for therapeutic alternatives