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Review

Over-the-counter anti-ageing topical agents and their ability to protect and repair photoaged skin

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ABSTRACT

Ultraviolet radiation (UVR)-induced photoageing of the skin is associated with characteristic clinical features including a sallow complexion, deep, coarse wrinkles and a loss of elasticity. Remodelling of the dermal extracellular matrix (ECM) with changes to fibrillar collagens, elastic fibres and glycosaminoglycans is likely to be a major contributing factor to these particular clinical signs. Over-the-counter (OTC) topical formulations are one popular management strategy for preventing and/or repairing photoaged skin, most commonly targeting wrinkles as these are often the most concerning clinical feature. Due to the cosmetic nature of such formulations, evidence of their clinical efficacy and mechanism of action is often limited. However, these formulations usually contain putative active ingredients which individually have been subject to *in vitro* and *in vivo* investigation for efficacy as photoageing interventions. This review highlights commonly found ingredients within OTC formulations and assesses the evidence for: (i) their efficacy in clinically and histologically improving photoaged skin; (ii) the potential mechanisms of action; and (iii) their ability to act synergistically with complementary ingredients to enhance the clinical outcome.

Contents

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1. Introduction

Skin ageing is a complex and cumulative process in which the effects of intrinsic (chronological) and extrinsic (externally driven) ageing may be overlaid. As extrinsic skin ageing is caused most commonly by chronic exposure to ultraviolet radiation (UVR); this is often referred to as photoageing. Clinically, photoaged skin is characterised by deep coarse wrinkles, roughened skin, mottled pigmentation and a marked loss of elastic recoil [1,2]. Histologically, photoageing manifests with a thickening of the epidermis [3] and significant remodelling of the dermal extracellular matrix (ECM), which is thought to underlie clinical features such as wrinkles and loss of elastic recoil. During photoageing the three major classes of dermal ECM components - fibrillar collagens [1,4–6], elastic fibres [7–10] and glycosaminoglycans (GAGs; both free and protein-associated) [11,12] – are differentially remodelled, leading to changes in their relative molecular composition, architecture and hence function (Table 1). The most notable dermal changes are the early and specific loss of fibrillin-rich-microfibrils from the papillary dermis [8] followed by the subsequent loss of dermal collagen content [1,4], a build-up of dystrophic elastotic material within the deeper dermis [7,13,14] and an accumulation of disorganised GAGs, most notably chondroitin sulphate and hyaluronic acid (HA), in these areas of solar elastosis [12] (see Naylor et al. [15] for comprehensive review of ECM turnover in instrinsic and photoaged skin).

Dermal photoageing is induced mainly by exposure to UVR through a number of proposed mechanisms, the most widely documented being matrix metalloproteinase (MMP)-driven degradation. Ultraviolet radiation has been found to increase the synthesis and activity of MMPs [16–22] but not their inhibitors (tissue inhibitors of MMPs; TIMPS) [19,23] leading to a degradative environment within the ECM. Reactive oxygen species (ROS) induced by UV irradiation [24–27] are also thought to play a role in dermal remodelling, potentially acting as signalling intermediates leading to activation of certain MMPs including MMPs-1 [16,28,29], -3 [23,30] and -9 [21], alongside directly degrading dermal ECM proteins [31]. In addition, UVR may act directly to preferentially degrade proteins which are rich in UVR-absorbing chromophores [32,33] and hence may drive some of the early events in photoageing such as the specific loss of the microfibril components fibrillin-1 [8] and fibulin-5 [34] from the papillary dermis. It has recently been hypothesised that this absorption of UVR by chromophore-rich proteins may also instigate the aforementioned indirect cellular routes of dermal matrix remodelling, *via* the photodynamic production of ROS and the subsequent up-regulation and/or activation of MMPs, leading to further matrix degradation [35].

As dermal ECM remodelling is a key contributing factor to the clinical features of photoageing it is essential that these changes, along with the underlying UVR-mediated mechanisms, are either prevented or reversed in order for photoaged skin to be managed effectively. Over-the-counter (OTC) topical anti-ageing formulations are one popular management strategy. Due to their cosmetic nature, and therefore not under the same stringent regulation as drugs, evidence of the clinical efficacy and mechanism of action of these formulations is often limited. However these formulations contain active ingredients which individually have been subject to at least *in vitro* analysis of their effect on key photoageing markers, with a limited number assessed for their effects on the clinical aspects of photoaged skin. This review will discuss both the potential mechanisms *via* which these ingredients may act and evidence for their efficacy in improving the clinical and histological aspects of photoaged skin. In addition, novel compounds which could potentially be used in OTC formulations will also be discussed. This article is not a systematic review but highlights commonly found ingredients within 'anti-ageing' cosmetics.

Table 1
All three major components of dermal ECM – collagens, elastic fibres and the GAG content – undergo significant alterations during the process of photoageing. These are thought to lead to many of the major clinical features of photoaged skin, including a lax appearance and the development of deep wrinkles associated with a loss of skin elasticity.

	Change in composition and architecture	Proposed functional and clinical consequences
Collagen network	Marked loss of collagen I and III content of dermis [1,4]. Reduced collagen VII anchoring fibrils beneath DEJ [5]	Reduced tensile strength [6]. Increased wrinkle formation [5]
Elastic-fibre network	Accumulation of disorganised elastotic material in the reticular dermis [7] with a 'grentz zone' beneath the DEJ with a greatly reduced amount of fibrillin-rich-microfibrils [8]	Reduced elastic recoil [9]. Contributing factor to wrinkle development [10]
GAG content	Some studies suggest decreased HA content due to alterations in GAG binding ability [11]. Other studies observe increased GAG content which is associated with solar elastosis [12]	Changes in skin hydrophilicity may affect tissue hydration and hence skin mechanical properties and appearance [12]

1.1. Individual components in topical interventions for photoaged skin

There are many topical formulations available OTC which claim to improve the appearance of photoaged skin. These products are complex, containing a wide range of putative active ingredients. Despite this, it is possible to group commonly found ingredients within OTC products based on their chemical nature, and to a lesser extent on their proposed mechanism of action.

1.1.1. All-trans retinoic acid is gold standard treatment

The 'gold standard' topical clinical treatment for photoaged skin is all-*trans* retinoic acid (*t*-RA), a biologically active form of vitamin A [36] which can significantly improve the clinical appearance of facial wrinkles [37,38]. Histological studies have shown that application of *t*-RA to the skin increases: (i) the amount of collagen types I and III within photoaged dermis [39]; (ii) the number of collagen VII anchoring fibrils at the DEJ [40] and; (iii) both the expression of