*Commentary*
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# Treating cutaneous aging with patented technologies

## 1. Introduction

Cutaneous aging is a multifactorial process affecting different constituents of the skin (Reddy and Gilchrest 2011). During aging, distribution of subcutaneous fat is altered. The subcutaneous fat is significantly lost from the dorsum of the hand, face and shin, but accumulates in the waist or thigh (Kligman *et al.* 1985; Farage *et al.* 2007). In the epidermis, signs of aging include lowering of the levels of collagen IV and collagen VII at the basement membrane, flattening of the rete ridge, thinning of the epidermis, and lowering of the levels of ceramides, free fatty acids, squalene and epidermal cholesterol (El-Domyati *et al.* 2002; Hayashi *et al.* 2003; Sandby-Moller *et al.* 2003; Neerken *et al.* 2004; Fore 2006). In the dermis, aging leads to fragmentation of elastin, an increase in collagen degradation, and a decrease in production of dermal collagen, proteoglycans and glycosaminoglycans (Giacomoni *et al.* 2000; El-Domyati *et al.* 2002; Carrino *et al.* 2003; Fore 2006; Varani *et al.* 2006; Farage *et al.* 2007). Owing to atrophy of the supporting dermis, the skin hydration level and skin repair capacity are reduced (Farage *et al.* 2009). Elderly people, therefore, are predisposed to susceptibility to skin injuries and disorders (including altered wound healing, immunologic changes, dermatologic diseases, and skin cancers).

Along with the increasing understanding of the mechanism of cutaneous aging, opportunities have been brought to research into anti-aging treatment. In an earlier study, oral administration of isotretinoin was found not only to improve skin thickness, skin colour, skin elasticity and skin tone, but also to reduce pigmented lesions, mottled hyperpigmentation and wrinkles (Hernandez-Perez *et al.* 2000). More recently, caloric restriction has been reported to prevent or delay age-associated histomorphological changes by reducing the age-related increase in the depth of the epidermis, dermis, and fat layer, and by increasing the collagen percentage, elastic fiber fraction area and dermal fibroblast population (Bhattacharyya *et al.* 2005). These are only few examples of the large number of works devoted to skin rejuvenation over the past 20 years. More examples of approaches explored for treatment of aging skin are listed in table 1. These approaches can be categorized into cosmetic procedures and cosmeceutical interventions. Many of them have been evaluated clinically for skin treatment (Beer 2011; Blyumin-Karasik *et al.* 2011; Yokoyama *et al.* 2014). Apart from the advances reported in the scientific literature, innovations reported in the patent literature are also worth noticing. As these innovations may not have been documented in scientific journals due to the issue of intellectual property, patent publications are a rich knowledge source complementary to the conventional scientific literature.

## 2. Cosmeceuticals in the patent literature

As far as the patent literature on cutaneous aging is concerned, the number of patents on cosmeceuticals much exceeds that on cosmetic procedures. This may be because cosmeceuticals in general are more convenient for self-application and are less invasive (McCullough and Kelly 2006). This gives cosmeceuticals a higher practical potential. In 2011, a patent was published on a composition comprising a dill extract, a blackberry leaf extract, and a cosmetically acceptable carrier (Kizoulis *et al.* 2011). *In vitro* studies showed that the blackberry extract stimulates tropoelastin production (Kizoulis *et al.* 2011). Compared to a composition containing either a dill extract or a blackberry leaf extract, the one containing

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**Table 1.** Some commonly used approaches for treatment of cutaneous aging

| Approach | Modes of action | References |
|---|---|---|
| **Cosmetic Procedures** | | |
| Injection of botulinum toxin | Temporarily paralyzing selected facial muscles, thereby reducing unwanted lines | Ascher *et al.* 2004; Carruthers *et al.* 2002 |
| Chemical peels | Exfoliating the aged skin chemically | Camacho 2005; Kadhim and Al-Waiz 2005; Nikalji *et al.* 2012 |
| Dermabrasion | Using controlled surgical scraping to remove the entire epidermis and the upper/mid dermis | El-Domyati *et al.* 2004; Karabekmez *et al.* 2013 |
| Injection of dermal fillers | Augmenting soft tissues by injecting dermal fillers so as to tackle skin atrophy and rhytides | Werschler and Weinkle 2005 |
| Nonablative photorejuvenation | Selectively confining thermal injuries to the papillary and upper reticular dermis, with an aim to stimulate fibroblast activation and to facilitate synthesis of new collagen and extracellular matrix materials | Longo *et al.* 2013; Nelson *et al.* 2002 |
| **Cosmeceuticals** | | |
| Coenzyme Q10 | Counteracting the age-associated increase in cellular oxidation, and preventing inflammation induced by UV radiation | Fuller *et al.* 2006; Prahl *et al.* 2008 |
| Ferulic acid | Inhibiting UVB-induced erythema, scavenging free radicals, and stabilizing antioxidant vitamins such as vitamin C | Saija *et al.* 2000; Staniforth *et al.* 2012; Thiele 2001 |
| Green tea polyphenols | Neutralizing reactive oxygen species, and exhibiting immunomodulatory effects | OyetakinWhite *et al.* 2012 |
| α-hydroxy acids | Decreasing the thickness and pH of the stratum corneum, enhancing desquamation by inhibiting kinases and transferases in desmosomes, promoting collagen and elastin synthesis, and increasing the concentration of glycosaminoglycans | Bernstein and Uitto 1995; Rona *et al.* 2004; Yamamoto *et al.* 2006 |
| Idebenone | Scavenging free radicals, and increasing skin hydration | McDaniel *et al.* 2005 |
| Retinoids | Promoting *de novo* collagen synthesis and angiogenesis, increasing the levels of TGF-β and glycoproteins, and stimulating mitotic and fibroblast activity | Afornali *et al.* 2013; Herschthal and Kaufman 2007; Kafi *et al.* 2007 |
| Vitamin C | Counteracting free radical production, and inducing regeneration of vitamin E30 and vitamin E31 | Fitzpatrick and Rostan 2002; Holck and Ng 2003 |
| Vitamin E | Inhibiting lipid peroxidation and interrupting free radical chain reactions | Meltzer and Watson 2013 |
| Zinc | Functioning as an important cofactor of superoxide dismutase, which is a powerful enzymatic antioxidant | Kumar *et al.* 2012 |

both extracts improved skin elasticity much more significantly in clinical trials (Kizoulis *et al.* 2011). Notwithstanding this apparent success, the sample size of the experimental group was rather small (around 25). Detailed evaluation of the effects of socio-demographic factors (such as gender, age and ethnicity) on the effectiveness of the composition was also lacking. In order to confirm the practical utility of the composition, more clinical evaluation is necessary. Another composition showing a cosmetic potential is the one reported by Golz-Berner and Zastrow (2011). Its major components include a fig extract, a pomegranate extract, rosemary powder, melon liposomes, plankton liposomes and lysate liposomes. As judged by subjects using the composition for four weeks, the composition could moisturize the skin, restore skin elasticity, and reduce fine lines (Golz-Berner and Zastrow 2011). Due to the lack of a comparable control group, more research, however, is needed to exclude the placebo effect and other factors (such as changes in the subjects' health behaviour).

Apart from the aforementioned, there are other patented compositions showing encouraging anti-aging performance. For instance, a composition containing *Hibiscus esculentus* extracts was reported to lessen skin wrinkles clinically (Han *et al.* 2011). The effect of the composition may be due to the presence of *Hibiscus esculentus* extracts, which were shown to stimulate muscle relaxation in a rat diaphragm model and to increase collagen biosynthesis in human fibroblasts (Han *et al.* 2011). Recently, a composition comprising the following ingredients has also been found to facilitate stratum corneum renewal, thereby improving the visual appearance, function and biophysical properties of the skin (Schiltz 2012): magnesium ascorbyl phosphate; lemon and cucumber extracts; propylene or butylene glycol; water; a chelating agent (e.g. ethylene diamine tetraacetate); a cationic surfactant (e.g. *N*,*N*-dimethyldodecyl amine oxide); and a anionic surfactant (e.g. sodium dodecyl sulfate and monoalkyl phosphate). The encouraging performance of these compositions has endowed these patented innovations with a potential for cosmetic and therapeutic applications.

Over the last several decades, an increasing number of agents capable of confronting cutaneous aging have been recognized. One example is the pomegranate fruit extract, which inhibits the death of UV-irritated human skin fibroblasts by reducing activation of NF-κB, down-regulating caspase-3, reducing the level of UV-induced reactive oxygen species, and escalating the intracellular antioxidant capacity (Pacheco-Palencia *et al.* 2008). Another example is trans-3,4′,5-trihydroxystilbene (also known as resveratrol), which is a polyphenolic phytoalexin that imparts its skin protective effects against photoaging by modulating the cki–cyclin–cdk network and MAPK pathway (Staberg *et al.* 1983; Miller and Weinstock 1994; Afaq and Mukhtar 2006). More recently, several medicinal herbs (such as *Hu-Ji-Chi*, *Ding-Di-Wu-Gong*, *Nan-Ling-Yia-Hua*, and *Ci-Yeh-Suei-Ding-Hsiang*) have been demonstrated to exert melanin formation-inhibiting effects, 2,2-diphenyl-1-picrylhydrazyl (DPPH) free-radical scavenging effects, elastase-inhibiting effects and superoxide dismutase-like effects (Aiyama *et al.* 2012). These herbs are worth further exploration for retardation and prevention of cutaneous aging. In fact, besides those mentioned above, there are many more agents that have been adopted for treatment of aging skin. Some of those used in issued patents are listed in table 2. Although more rigorous evaluation is required to evaluate their efficiency and safety, these agents are candidates for screening and for future development of skin treatment.

## 3. Prospects for preventive anti-aging measures

Compared to treatment, prevention is more cost-effective and humane (Weinstein 1990). At this moment prevention of cutaneous aging can be achieved only by photoprotection or anti-oxidant supplementation. Since the turn of the last century, significant advances have been made in technologies for nucleic acid delivery (Lai and Lin 2009; Lai 2011a, 2014, 2015). Recently, a patent relating to a transdermal nucleic acid delivery system has been published (Kaspar 2013). That system comprises neutral lipids and an alcohol at a ratio of 2.5:1–3:1 by weight, and can significantly enhance transdermal gene delivery upon topical application. Furthermore, a pulsed electric field has also been reported in the patent literature to target genes to the epidermis (Dev *et al.* 2013). As recent patents relating to therapeutics delivery have been reviewed elsewhere (Lai 2011b), we are not going to dwell into it further. But it is worth stressing that the intrinsic process of skin aging is largely genetically programmed, abilities to deliver exogenous nucleic acids to skin imply the possibility that the genetic process of aging at the molecular level can be modulated and the intrinsic process of skin aging can be halted proactively (Lai 2013).

**Table 2.** Some agents exploited in the patent literature for treatment of cutaneous aging

| Agent | Patent | Inventor(s), Year |
|---|---|---|
| *Adiantum flabellulatum* extract | US8101211 B2 | Chiba *et al.* 2012 |
| *Aloe vera* gel | US 6426081 B1 | Chong 2002 |
| *Anisomeles indica* extract | US8101211 B2 | Chiba *et al.* 2012 |
| Banyan tree serum | US8486461 B2 | Swanson *et al.* 2013 |
| Basic fibroblast growth factor | US8518878 B2 | Ono 2013 |
| *Boehmeria densiflora* extract | US8101211 B2 | Chiba *et al.* 2012 |
| *Brassocattleya marcella* Koss orchid extract | US 8293287 B2 | Cauchard *et al.* 2012 |
| *Bredia oldhami* extract | US8101211 B2 | Chiba *et al.* 2012 |
| *Castanea sativa* extract | CA2772626 C | Burke-Colvin *et al.* 2013 |
| *Chromolaena odorata* extract | EP 1367988 B1 | Donovan 2007 |
| *Clerodendrum cyrtophyllum* extract | US8101211 B2 | Chiba *et al.* 2012 |
| Clover serum | US8486461 B2 | Swanson *et al.* 2013 |
| Copper-zinc malonate | CA2641420 C | Ramirez and Faryniarz 2013 |
| Creatine compounds | CA2376943 C | Kaddurah-Daouk 2010 |
| *Drosera burmanni* extract | US8101211 B2 | Chiba *et al.* 2012 |
| *Elaeagnus oldhamii* extract | US8101211 B2 | Chiba *et al.* 2012 |
| (-)epigallocatechin-3-gallate | EP1727512 B1 | Cho *et al.* 2011 |
| *Euphorbia formosana* extract | US8101211 B2 | Chiba *et al.* 2012 |
| *Eurohorbia hirta* extract | US8101211 B2 | Chiba *et al.* 2012 |
| *Euterpe oleracea* extract | CA2772626 C | Burke-Colvin *et al.* 2013 |
| Extract of *Bertholletia excelsa* | US 6471972 B1 | Bonte *et al.* 2002 |
| Extract of chick peas | CA 2299457 C | Pillai *et al.* 2008 |
| Extract of *Ficus erecta* var. *beecheyana* | US8101211 B2 | Chiba *et al.* 2012 |
| Extract of *Glycine max* | US 6471972 B1 | Bonte *et al.* 2002 |
| Extract of *Medicago sativa* | US 6471972 B1 | Bonte *et al.* 2002 |
| Extract of *Portulaca oleracea* | US 7060303 B2 | Jones 2006 |
| Extract of *Potentilla erecta* | US 6471972 B1 | Bonte *et al.* 2002 |
| Extract of *Torenia concolor* var. *formosana* | US8101211 B2 | Chiba *et al.* 2012 |
| Fruit extracts of plants of the Ericacea family | US7470438 B1 | Fagot 2008 |
| Ginsenoside F1 | EP1727512 B1 | Cho *et al.* 2011 |
| *Gossypium hirsutum* extract | CA2772626 C | Burke-Colvin *et al.* 2013 |
| Gum mastic | US 6623728 B2 | Harichian *et al.* 2003 |
| 7-hydroxy-dehydroepiandrosterone | US 6994864 B2 | Breton 2006 |
| *Ilex paraguariensis* leaf extract | US8529925 B2 | Alexiades-Armenakas 2013 |
| *lpomoea pes-caprae* extract | US8101211 B2 | Chiba *et al.* 2012 |
| Isosorbide | EP1891929 B1 | Miura and Haratake 2012 |
| 7-keto-dehydroepiandrosterone | US 6994864 B2 | Breton 2006 |
| *Kummerowia striata* extract | US8101211 B2 | Chiba *et al.* 2012 |
| Lactobacillus ferment | CA2772626 C | Burke-Colvin *et al.* 2013 |
| Lotus serum | US8486461 B2 | Swanson *et al.* 2013 |
| *Ludwigia hyssopifolia* extract | US8101211 B2 | Chiba *et al.* 2012 |
| *Ludwigia octovalvis* extract | US8101211 B2 | Chiba *et al.* 2012 |
| Methylsilanol mannuronate | CA2772626 C | Burke-Colvin *et al.* 2013 |
| Micrococcus lysate | US8529925 B2 | Alexiades-Armenakas 2013 |
| *Mussaenda parviflora* extract | US8101211 B2 | Chiba *et al.* 2012 |
| Palmitoyl tetrapeptide-7 | CA2772626 C | Burke-Colvin *et al.* 2013 |
| *Punica granatum* extract | CA2772626 C | Burke-Colvin *et al.* 2013 |

**Table 2** (continued)

| Agent | Patent | Inventor(s), Year |
|---|---|---|
| Quaternary ammonium polyol salts | CA2584468 C | Harding and Harichian 2013 |
| Red yeast rice extract | US 6395281 B1 | Januario *et al.* 2002 |
| Retinyl diphenyl glycolate | US 6180670 B1 | Duffy *et al.* 2001 |
| Retinyl glycolic ether | US 6180670 B1 | Duffy *et al.* 2001 |
| Retinyl lactate | US 6180670 B1 | Duffy *et al.* 2001 |
| Retinyl mandelate | US 6180670 B1 | Duffy *et al.* 2001 |
| Retinyl salicylate | US 6180670 B1 | Duffy *et al.* 2001 |
| S-acyl glutathione derivative | US8609604 B2 | Perricone 2013 |
| *Sapium sebiferum* extract | US8101211 B2 | Chiba *et al.* 2012 |
| *Scutellaria rivularis* extract | US8101211 B2 | Chiba *et al.* 2012 |
| *Silybum marianum* extract | US 6524599 B2 | Pinnell 2003 |
| *Sphenomeris chusana* extract | US8101211 B2 | Chiba *et al.* 2012 |
| *Staurogyne concinnula* extract | US8101211 B2 | Chiba *et al.* 2012 |
| *Tanacetum parthenium* extract | EP1367993 B1 | Martin and Saliou 2007 |
| *Tetrastigma dentatum* extract | US8101211 B2 | Chiba *et al.* 2012 |
| Thymosin 134 (Tβ4) | EP1335743 B1 | Goldstein 2009 |
| 3,3′,5,5′-tetrahydroxystilbene | US6414038 B2 | Maignan 2002 |
| *Verbana officinalis* extract | US8101211 B2 | Chiba *et al.* 2012 |
| *Vermonia cinerae* extract | US8101211 B2 | Chiba *et al.* 2012 |
| *Vitex negundo* extract | US8101211 B2 | Chiba *et al.* 2012 |
| Trifluoromethylketone derivatives | US6610748 B1 | Yabuta *et al.* 2003 |
| *Uncaria hirsuta* extract | US8101211 B2 | Chiba *et al.* 2012 |

## 4. Concluding remarks

Cutaneous aging is caused by a combination of intrinsic aging and extrinsic factors such as cigarette smoke, pollution, and UV damage. Along with the gradual disentanglement of the molecular mechanism of cutaneous aging over the last several decades, encouraging progress has been made in skin rejuvenation. Despite this, significant attention has focused on advances published in the scientific literature. Works in the patent literature have always been overlooked. As a matter of fact, the patent literature is a repository of knowledge complementary to the scientific literature. It can be a source of insights for future development of anti-aging medicine. Given its limited scope, this commentary is by no means a comprehensive account of all patents on treatment of aging skin. However, with the overview of innovations we have presented, it is our wish to have more awareness being brought to the possible contributions of the patent literature to future development of anti-aging medicine.

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