Topical Vitamins, Minerals and Botanical Ingredients As Modulators of Environmental and Chronological Skin Damage

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Abstract and Introduction

Abstract

Ageing skin is characterized by fine lines, wrinkles, lentigines, dyspigmentation and increased coarseness. Topical preparations alleged to combat these changes abound in the over-the-counter market. Some of the most popular ingredients used in these products are vitamins, minerals and botanical extracts. Proposed mechanisms for antiageing effects on skin range from antioxidant properties to improved collagen synthesis or protection from collagen breakdown. Despite the media attention and consumer popularity that these ingredients have generated, there have been few scientific studies to support these claims. In this report, we review recent published studies on the most common of these ingredients for the topical photoprotection and the treatment of ageing skin.

Introduction

Environmental or exogenous factors such as ultraviolet (UV) radiation, wind and smoke contribute to the extrinsic ageing of skin. This type of ageing, combined with intrinsic, or chronological ageing, results in the degeneration of the skin barrier, the development of rhytides, discoloration and possible malignant degeneration, among other changes.[1,2] Cosmetic changes associated with ageing, especially on the face, are particularly concerning to a patient population which wishes to remain looking youthful. As the demand for products that reduce the cosmetic effects of ageing continues to grow, healthcare professionals have a responsibility to educate themselves and to become informed about the scientific basis and established data, if any, behind these products. Clearly, topical, over-the-counter products alleged to benefit ageing skin are immensely popular among patients. These products account for annual sales of over 2 billion dollars in the U.S.A. alone.[3] Although topical medications such as tretinoin have been demonstrated in the scientific literature to reduce the signs of ageing,[4,5] patients often seek over-the-counter antiageing products due to the market availability, comparably cheaper prices, and the lack of the physician bottleneck.

Recently, consumer and media attention has focused specifically on products utilizing 'natural' ingredients such as vitamins, minerals and botanical extracts. These ingredients have the appeal of appearing wholesome and 'organic'. Although scientific evidence shows that some of these ingredients do have possible *in vitro* antiageing activity, the question remains whether it is possible to deliver adequate doses to the skin *in vivo.* and to produce either histological or clinical improvement of wrinkles, lentigines, coarseness, pigmentary changes, dryness and other characteristics of ageing skin. This article reviews recent published studies on the most common of these 'natural ingredients' and summarizes their proposed effects on ageing skin.

Methods

The Medline electronic database was searched from 1996 to 2002 using the following keywords: vitamins, minerals, botanical extracts, tea extracts, herbal, vitamin E, alpha-tocopherol, vitamin C, ascorbic acid, retinol, retinal, nicotinamide, niacinamide, coenzyme Q10, *Ginkgo,* grape seed extract, lemon, lavender, ginseng, rosemary, green tea, soybean, genistein, seaweed, peppermint, algae, cucumber, aloe vera, wheat protein, witch hazel and panthenol, cross-matched with the key words ageing/aging and skin. The bibliographies of these papers were then scanned for relevant references which form the basis of this report.

Because the topic is broad, this review is limited to recent reports, as well as older studies which utilized human subjects, established background information for recent reports, or demonstrated a particularly important research

finding.

Vitamin E (a-Tocopherol)

Vitamin E is one of the better established ingredients in over-the-counter treatments of skin ageing. Vitamin E, or a-tocopherol, is a lipid-soluble antioxidant which plays key roles in protecting cellular membranes from lipid peroxidation by free radicals.[6,7] These free radicals contribute significantly to the environmental, or exogenous ageing of skin, especially UV-mediated damage.[8] Although the human skin possesses various intrinsic defence systems which help to mitigate these types of oxidative damage, both excessive and chronic exposure to free radicals can deplete the body's defence. Free radicals cause the disruption of normal biomolecules such as lipids, proteins and nucleic acids, as well as deplete the body's own endogenous antioxidants.[9] Antioxidants, such as a-tocopherol, modulate this damage by scavenging free radicals and lipid peroxyl radicals.[10]

Interestingly, vitamin E is distributed in a gradient fashion in the stratum corneum of healthy skin, with the highest levels in the deepest layers and the lowest levels closest to the surface.[10] In a recent review of antioxidants in the skin, Thiele *et al.* concluded that a-tocopherol is the major antioxidant in the human epidermis, and that its depletion is an early and sensitive marker of environmental oxidative damage.[11] Vitamin E is available over-the-counter in various forms, most commonly as a-tocopherol or tocopherol acetate. However, as with other vitamins and antioxidants applied topically, success of delivery and clinical efficacy are separate and crucial elements of an effective antiageing treatment. This was demonstrated in a human study in which the acetate form of tocopherol showed no evidence of conversion to the biologically active form, a-tocopherol, despite adequate absorption into the skin.[12] Further, a recent study on the metabolic conversion of a-tocopherol acetate into a-tocopherol in skin demonstrated that permeation and metabolism of a-tocopherol acetate was highly dependent on the delivery system, re-emphasizing the importance of formulation in cosmetic preparations.[13]

In a rare hemiface trial with human subjects, 5% vitamin E was better than a vehicle control in reducing rhytides, skin roughness, length of facial lines and depth of wrinkles as measured by optical profilometry.[14] Gehring *et al.* demonstrated that the topical application of vitamin E increased stratum corneum hydration and enhanced water-binding capacity.[7] In various *in vitro* experiments by Ricciarelli *et al.* a-tocopherol reduced the age-dependent increase of collagenase expression by inhibiting protein kinase C activity.[15]

The protective effects of vitamin E against photoageing have been demonstrated in various animal and *in vitro* skin models. In hairless mice, topical vitamin E has been shown to decrease the severity of UV-induced skin wrinkling by 75% and significantly to reduce erythema and oedema.[16,17] Similar photoprotective effects were evident in experiments on pig skin.[18] A study using a topical vitamin E analogue, Trolox, showed inhibition of UVB-induced intracellular peroxide generation in human keratinocytes.[19] However, results from various studies conflict over whether vitamin E applied after UV exposure can mitigate UV-induced erythema and oedema. Although some animal studies support the benefit of vitamin E by diminishing UV-related responses of the skin, a recent trial using human subjects failed to demonstrate benefits when vitamin E was applied after UV exposure.[20] Hence, although vitamin E has thus far yielded promising results for the treatment of both intrinsic and extrinsic ageing, very few of these studies have used human subjects.

Vitamin C

Vitamin C has gained mass popularity in the last few years as an over-the-counter ingredient for the treatment of photoageing. l-ascorbic acid, the biologically active form, has well-established roles in the human body as an antioxidant and as a cofactor for collagen synthesis.[21,22] Ascorbate participates in the hydroxylation of procollagen, and studies show that it may also stimulate collagen synthesis directly by activating its transcription and stabilizing procollagen mRNA.[21,23] An *in vitro* study showed collagen biosynthesis to be inversely related to the age of donor human fibroblasts, but that stimulation of collagen synthesis by ascorbic acid was independent of fibroblast age.[24] As an antioxidant, ascorbic acid is the body's main water-soluble, nonenzymatic electron scavenger, enabling it to function efficiently in aqueous compartments.[22] In addition to these roles in the maintenance of skin health, ascorbic acid also helps to regenerate the oxidized forms of a-tocopherol.[25,26] These properties of ascorbic acid are the basis for the antiageing claims made by the skincare industry. However, because it is water-soluble, topical preparations of vitamin C have been difficult to stabilize in solution and to formulate in a manner that adequately penetrates the skin.[22]

In one of the very few published reports on the effects of topical 'natural' skincare products in a placebo-controlled clinical trial, Traikovich found that topical ascorbic acid in the form of Cellex-C applied for 3 months showed a 73.7% improvement in optical profilometry image analysis.[27] This study compared a randomized hemiface application of ascorbic acid with a vehicle control, and demonstrated significant improvements in clinical, subjective and photographic assessments of wrinkling, roughness, rhytides, laxity and sallowness.

The physiological mechanisms affected by vitamin C are likely to include the increased production of collagen as well as the decreased production of matrix metalloproteinase, an enzyme which enhances dermal collagen degradation.[28] In a randomized, blinded human study, 5% vitamin C was applied to one forearm, while placebo was applied to the other for 6 months. Skin biopsies showed increased mRNA levels of collagen I, collagen III and tissue inhibitor of matrix

metalloproteinase 1 on the side treated with vitamin C. Interestingly, the results were most remarkable in subjects with lower dietary intake of the vitamin. However, in this same study, mRNA levels of elastin, fibrillin and tissue inhibitor of matrix metalloproteinase 2 were not significantly affected.[29]

Alster and West propose that ascorbic acid may also have some anti-inflammatory effects, as suggested by its ability to reduce post-CO_2 laser-induced erythema, a clinical indicator of dermal inflammation caused by laser injury.[30] Further, its role as an antioxidant gives ascorbate similar photoprotecting properties as vitamin E by neutralizing UVB-generated free radicals. Darr *et al.* demonstrated in pigs the reduction of both UVB-induced erythema and histological sunburn cells by pretreatment with 10% ascorbic acid.[31] Ascorbate may also have similar protective effects against UVA, as the investigators also showed a reduction of sunburn cells in UVA-exposed porcine skin presensitized with psoralen.[31] Various other models using human skin have demonstrated similar effects either with ascorbate alone, or in combination with vitamin E.[32,33] These results have been also corroborated in a small study with 10 human subjects.[34]

In the hairless mouse, both topical vitamin E and vitamin C reduced UVB-induced skin wrinkling. However, UVA-induced sagging was unaffected.[17] Beyond its well-known antioxidant effects, Catani *et al.* suggest that vitamin C may also have cytoprotective effects by inhibiting activator protein-1, a gene transcription activator induced by UV irradiation which results in keratinocyte cell death.[35] Further, Takashima *et al.* found that vitamin C as ascorbyl phosphate may have some efficacy in the lightening of skin dyspigmentation.[36]

Studies show that vitamin C clearly has numerous roles in the maintenance of skin health, and may prove to be an important mediator of cutaneous ageing. However, inconsistencies in product stability and difficulties in the adequate penetration of skin limit the topical efficacy of many, if not most, of the skincare products containing vitamin C. The most common forms of vitamin C found in cosmetic products are l-ascorbic acid, and its ester form ascorbyl palmitate. Topically applied l-ascorbic acid increased ascorbate levels in pig skin up to 25 times.[31] However, ascorbic acid has been notoriously difficult to stabilize, as it rapidly oxidizes in solution. More recently, stable and hydrophobic solutions of ascorbic acid have been developed consisting of the molecule in its nonionized form at a low pH.[37] Ascorbyl palmitate, which is the fat-soluble form of ascorbic acid, is not as well established in its stability and penetration, but was found to be 30 times more effective than ascorbic acid when acting as a tumour inhibitor in mouse skin.[38]

In summary, although vitamin C appears to be a promising cosmetic ingredient, larger studies with human subjects need to be done before the role of vitamin C in skin ageing can be firmly established, and a stable, skin-penetrating compound can be documented.

Vitamin A As Retinol

Retinoids function in the normal maintenance of epidermal differentiation and growth.[39,40] Various retinoid receptors, when bound with retinoid ligands, act as important transcription factors in the human cell.[41] Deficiency of dietary vitamin A results in generalized xerosis, hyperkeratosis and squamous metaplasia of mucous membranes.[42] In the treatment of photoageing, numerous large-scale, double-blinded, placebo-controlled trials have shown the efficacy of topical tretinoin.[4,43,44] However, as tretinoin remains a prescription drug, over-the-counter products mainly utilize the vitamin A derivatives retinol and retinyl palmitate. These forms are not biologically active until enzymatic conversion to the principal active metabolite, retinoic acid.[45] Whether the skin has adequate levels of these conversion enzymes to make a clinically apparent difference has yet to be proven. Many of the studies discussed here are *in vitro* and do not address this issue of possible enzyme saturation directly. There are surprisingly few published studies focused on the over-the-counter retinoids, considering their widespread use. Although it is well established that UV irradiation decreases both retinol and retinyl ester levels in the epidermis, whether these decreases can be overcome by topical application is not understood.[46] Further, how the photoinactivation of vitamin A in human skin affects the topical supplementation of vitamin A is also not well addressed in the current literature.[47]

Researchers suggest that cutaneous ageing results from the interplay of extrinsic damage by UV radiation, intrinsic increases in collagen-degrading matrix metalloproteinases, and decreased collagen synthesis.[48] It is believed that retinol plays important roles in countering these mechanisms.[49,50] A study utilizing human skin samples found that topical 1% retinol inhibits the increase in metalloproteinases and stimulates collagen synthesis in both aged, sun-protected skin and in photoaged skin. Varani *et al.* also used tissue specimens to show that retinol may be able to restimulate fibroblast growth potential, which seems to decrease with increasing age.[51] Further, Kang *et al.* showed that topical retinol does increase epidermal thickness in human skin, but it was 20 times less potent than topical retinoic acid.[52] Evidence for the effectiveness and biological activity of the ester form of vitamin A, retinyl palmitate, is sparse, and no studies address clinically relevant findings in skin ageing. Further, in mice, retinol stores in the epidermis are partially UVB resistant, while retinyl esters were not.[46]

In an open study comparing the efficacy of vitamin E cream and 0.075% retinol, 14 volunteers followed a complex regimen involving the application of a vitamin E cream for a month, followed by retinol cream for 2 months, followed by vitamin E cream for another month. Samples of the stratum corneum during retinol treatment were shown to be less sensitive to sodium lauryl sulphate by corneosurfometry bioassay. UV squamometry tests and optical profilometry of UV-induced shallow wrinkling also demonstrated retinol to be more effective than vitamin E.[53]

Although some studies suggest the possible efficacy of retinol in improving the cosmetic appearance of ageing skin, over-the-counter products usually contain lower levels of retinol than used in these studies. Ultimately, because of variable retinol concentrations in cosmetic products and the lack of blinded clinical trials, the results of these studies should be interpreted carefully.

Other Vitamin-Based Ingredients (Nicotinamide and Coenzyme Q10)

Among the newer vitamin-based ingredients promoted by the cosmetic industry are nicotinamide (niacinamide) and coenzyme Q10 (ubiquinone). Studies on nicotinamide, a derivative of niacin, have mainly focused on its anti-inflammatory and antiacne vulgaris actions.[54,55] Researchers believe anti-inflammatory effects may ultimately improve skin appearance by reducing leucocyte peroxidase systems that may lead to localized tissue damage. Nicotinamide is a B vitamin and an integral part of the coenzymes nicotinamide adenine dinucleotide (NAD) and NAD phosphate. In a double-blinded study of 76 patients with acne vulgaris, 4% nicotinamide gel and 1% clindamycin gel were comparable in efficacy.[54] Tanno *et al.* showed that nicotinamide might have some utility in the treatment of chronological ageing by decreasing transepidermal water loss.[56] Further, sphingolipids, such as ceramides, are a major component of the stratum corneum,[57] and this *in vitro* experiment also preliminarily suggests that nicotinamide increases the activity of the rate-limiting enzyme involved in sphingolipid synthesis, as well as the mRNA levels of sphingolipids. When the investigators incubated keratinocytes with nicotinamide, increased levels of free fatty acids, cholesterol and ceramides were found in the stratum corneum.[56]

Published studies focusing on the possible antiageing effects of the mitochondrial electron transfer protein coenzyme Q10 are rare. Coenzyme Q10, otherwise known as ubiquinone, is an endogenous cellular antioxidant present in almost all the tissues of the body, including the skin.[10,25] It is believed that ubiquinone may have roles in both the extrinsic and chronological processes of ageing. Various authors have reported that the tissue levels of coenzyme Q10 decrease with age.[58,59] Hoppe *et al.* demonstrated this age-related reduction specifically in the skin.[60] The possibility that topical application of ubiquinone may help to stabilize or increase the decreasing levels of this antioxidant is the basis of the recent popularity of coenzyme Q10 in cosmetic products. In a study utilizing cultured human keratinocytes, cells pretreated with coenzyme Q10 had 60-70% less UVA-induced oxidative DNA damage than controls. The authors also demonstrated suppression of collagenase mRNA expression in coenzyme Q10-treated cells.[60] In 20 elderly volunteers, coenzyme Q10 applied on the periocular area resulted in a 27% reduction of wrinkle depth compared with a vehicle control applied to the other eye.[60] It is believed that topical application of coenzyme Q10 may treat extrinsic ageing by acting as an antioxidant counteracting UV damage, and also by replenishing the decreased endogenous levels of this antioxidant that have been lost with chronological ageing.

Tea Extracts

The leaf and bud of the plant *Camellia sinensis* are used to manufacture nonherbal teas such as green tea, black tea and oolong tea.[61] All three of these teas contain polyphenolic compounds that have significant antioxidant and anti-inflammatory activity.[62,63] Thus, these teas and their extracts, especially green tea, have become popular additions to topical skincare products. However, no clinical studies specifically investigating topical tea extracts and their cosmetic effects on ageing skin have been published to date.

The best data on tea extracts are on green tea polyphenols (GTPs).[64] Elmets *et al.* conducted a study in which volunteers were treated with topical green tea extract and then exposed to solar-simulated radiation. Clinically, certain GTPs were found to inhibit UV-induced erythema. Histologically, green tea-treated skin showed significantly reduced numbers of sunburn cells and had less depletion of the usually radiation-sensitive epidermal Langerhans cells. In this study, DNA damage assessed using a ^{32}P-postlabelling technique was decreased in green tea-treated skin.[65] Investigators have also shown UV-induced DNA pyrimidine dimers are reduced by pretreatment with topical GTPs.[66] In other studies, topical application of GTPs to human volunteers before UVB exposure decreased UVB-induced erythema, myeloperoxidase activity and leucocyte infiltration.[61,67] UV-induced lipid peroxidation was also shown to be inhibited by topical GTPs, which provided protection of intrinsic antioxidant systems in the human skin.[68] Recently, it was demonstrated that green tea may also have photoprotective effects against UVA radiation. Erythema occurred in human skin exposed to topical psoralen followed by UVA irradiation (PUVA). In contrast, skin similarly exposed to UVA and psoralen but pretreated with topical green tea at a dose of 0.2 mg cm^{-2} had less erythema.[69] Further, topical GTPs applied to various mouse models have shown significant protection against UV-induced skin tumorigenesis, chemical carcinogenesis and UVA-induced DNA damage.[70-72]

Murine studies show that black tea extracts may prove to have similar properties. The topical application of black tea extracts prior to UVB exposure reduced UVB-mediated erythema in both murine and human skin. In murine models, black tea extracts inhibited UVB-induced tyrosine phosphorylation of epidermal growth factor receptors and decreased the accumulation of the p53 oncogene.[73] Oolong tea contains similar polyphenols, and has recently been suggested as a treatment for recalcitrant atopic dermatitis because of its anti-inflammatory properties.[74] Although polyphenols and other tea extracts have demonstrable antioxidant activities that may benefit photoaged skin, it is not clear how these anti-inflammatory activities will translate into the cosmetic improvement of wrinkles and dyspigmentation of ageing skin.

Meanwhile, although tea extracts have the potential to be valuable products in the cosmetic industry, it is still unclear

how stable these properties are over time. Thus far, the evidence is still fairly weak, although future investigation may lead to more promising findings as active ingredients are isolated.

Botanical Extracts and Essential Oils

Botanical extracts are currently among the most common ingredients added to over-the-counter antiageing cosmetic preparations. Various botanical extracts were initially popularized for their possible aromatherapeutic potentials. More recent claims focus on the antioxidant properties of these extracts and their ability to modulate certain types of environmental damage.

The *Ginkgo biloba* plant, better known as a dietary supplement for the treatment of dementia and memory loss,[75,76] also has purported antiageing effects on skin. Fibroblasts incubated with various *G. biloba* extracts and ascorbic acid showed greater synthesis of collagen and extracellular fibronectin when compared with controls treated only with ascorbic acid.[77] Another reason for use of *Ginkgo* in cosmetic ingredients is the plant's antioxidant and anti-inflammatory properties. The *Ginkgo* plant contains various flavonoids, compounds which have free radical-scavenging activity and anti-inflammatory activities against cyclooxygenase and lipoxygenase.[78,79] Cytotoxicity was reduced in fibroblasts irradiated with UVB when they were pretreated with *Ginkgo* flavonoids such as quercetin and sciadopitysin.[80] Laboratory studies have documented a superoxide dismutase-like activity for *Ginkgo* extracts,[81] as well as an inhibitory role against lipoperoxidation.[82] Hibatallah *et al.*[83] utilized an inflammation model with methyl nicotinate on 10 volunteers, and found that *Ginkgo* extract containing 33% flavone glycosides reduced blood perfusion to the skin area by 37%. There is evidence that there is an optimal concentration for *Ginkgo* extract, above or below which its anti-inflammatory and antioxidant activities decrease.[83]

Grape seed extracts are rich in polyphenols, a few of which are similar to the polyphenols present in tea extracts.[84] However, most of the polyphenols differ from tea extracts and are collectively referred to as procyanidins. There are significant data supporting the antioxidant and anti-inflammatory activities of procyanidins,[85,86] as well as their role in promoting wound healing.[87] Grape seed polyphenols may also exert a stronger oxygen-scavenging effect than either vitamin C or vitamin E.[86,88] Zhao *et al.* utilized a mouse model to demonstrate grape seed polyphenol inhibition of epidermal lipid peroxidation at concentrations much lower than those previously reported for tea polyphenols.[89,90]

Lemon oil and lavender oil, traditionally used for their aromatic properties, have recently been investigated for their effects on skin. Calabrese *et al.*[91] isolated a component of lemon extract which, when applied to human skin, conferred increased resistance to oxidative stress. Skin surface lipids of the volunteers were examined by gas chromatography after the treatments. Further, this antioxidant activity of lemon oil extract was shown to be greater than that of a-tocopherol.[91] Lavender oil, probably the most popular of the botanical additives, has rarely been the subject of published reports. Most recently, Kim and Cho showed that topical lavender oil may inhibit immediate-type allergic reactions by reducing mast cell degranulation in rats.[92] Although there is hope that topical anti-inflammatory agents may benefit skin health by preventing intrinsic skin damage, there is no research establishing that this will ultimately translate into clinical reduction in the signs of ageing.

Ginseng is one of the most widely used medicinal plants, especially in the fields of traditional Eastern medicine. With growing awareness of alternative medicine, ginseng is gaining some popularity as a cosmetic ingredient. Although various ginseng extracts have a wide range of pharmacological activities, they are best known for their cytotoxic effects against tumour cells.[93,94] Despite the extensive investigations on the antioxidant and anti-inflammatory effects of ginseng, there are no studies on the role ginseng may play in the photoageing of skin. Studies on murine skin have described roles for ginseng in scavenging reactive oxygen intermediates and the inhibition of chemical tumour promotion.[95]

Rosemary extract is another botanical that has made the leap from herbal medicine to common cosmetic ingredient. Rosemary extract contains various antioxidants, such as compounds known as phenolic diterpenes.[96] Rosemary extract provided better oxidative protection of dehydrated chicken meat than both tea extract and grape skin extract, as measured by electron spin resonance spectrometry.[97] A study analysing the oxidative properties of human skin surface lipids after treatment with a rosemary extract showed decreased susceptibility to oxidative stress caused by the chemical oxidant t-butyl hydroperoxide.[97] Further, penetration into human skin is potentially favoured by the isolation of both hydrophobic and hydrophilic components of rosemary extract that have antioxidant activity.[96,98] Other possible roles for this common household plant include antitumour and anti-inflammatory activities.[99]

Rigorous research on botanical extracts is sparse at best. There is currently no proof that topical application of these botanical extracts results in clinical improvement of skin ageing. Laboratory and small-scale animal studies suggest that some botanical extracts do have measurable antioxidant or anti-inflammatory activities. However, variations in manufacturing practices, processing, growth media, seasonal environments, etc. limit the consistency of cosmetic products containing these ingredients. As with many of the vitamins and antioxidants discussed here, optimal conditions and concentrations for stability and clinical efficacy have not been established.

Soy Proteins

Protein extracts of soybeans and soymilk, including isoflavones such as genistein and daidzein, are among the most recent botanical agents to gain popularity in over-the-counter antiageing preparations. This recent surge of interest from the cosmetic industry is mostly based on studies utilizing mouse skin that suggest anticarcinogenic, antipigmentary and antioxidant properties in soy proteins.[100,101] Even more promising, genistein and daidzein appeared to increase hyaluronic acid production in human keratinocyte culture, and when topically applied to hairless mice, raised the intensity of hyaluronic acid staining in the murine dermis.[102]

Further, soy isoflavones are considered part of the phytoestrogen family, as recent data demonstrate conformational binding capacity for oestrogen receptors.[103] This finding has led to various product claims endorsing the oestrogen-like benefits of soy products in postmenopausal skin. However, the impact topical soy phytoestrogens may or may not have on either environmental or chronological skin ageing has yet to be characterized in any published scientific study.

What has been fairly well characterized in various studies includes the antiphotocarcinogenic properties of soybean isoflavones, especially genistein. In studies utilizing the hairless mouse, Wei *et al.* has shown that genistein exerts anticarcinogenic activities by blocking both the initiation and promotion of skin carcinogenesis via the prevention of DNA adduct formation and inhibition of various oxidative events.[100] The investigators also found that pretreating mouse skin with 10 µmol of topical genistein prior to UVB exposure significantly inhibited DNA oxidative damage compared with mouse skin treated with vehicle alone.[104] These photoprotective effects were also seen after UVA irradiation, when genistein applied to mouse skin substantially decreased PUVA-induced skin thickening, cutaneous erythema and skin ulceration. Immunohistochemical staining showed that the PUVA-induced increases in markers of DNA damage, such as caspase-3 and cleaved poly(ADP-ribose) polymerase, were also inhibited by topical genistein.[105]

Another soy component, the Bowman-Birk proteinase inhibitor (BBI), has been demonstrated to have multiple benefits, including *in vivo* radioprotective effects on skin fibroblasts.[106] Paine *et al.* showed that BBI and soybean trypsin inhibitor (STI) can prevent UV-induced pigmentation both clinically and histologically, when applied to dark-skinned pigs.[101] In a small clinical study with human subjects, Hermanns *et al.*[107] found significant clinical skin lightening after a 3-week treatment of five volunteers with soybean extract containing STI. The degree of skin depigmentation was comparable with that in patients treated with azelaic acid in the same study.

Compared with other botanical extracts discussed here, recent studies show that soybean extracts are among the more promising of the 'natural' ingredients utilized for cosmetic preparations that treat ageing skin. The combination of DNA-protective effects, antipigmentary capabilities and ability to boost hyaluronic acid levels in the skin may ultimately prove to provide some defence against the changes that occur in skin over time. However, as with all the ingredients reviewed in this paper, peer-reviewed, large-scale human studies still need to be pursued. Moreover, it is unclear what the oestrogen-like effects of soy products will mean to patients with a history of oestrogen-sensitive tumours, and whether significant systemic absorption of these phytoestrogens occurs with chronic topical application.

Other popular 'natural' cosmetic ingredients applied to ageing skin, but for which no references were found in a Medline search, are listed in Table 1.

Conclusions

Many studies strongly suggest that some over-the-counter cosmetic ingredients, such as vitamins, minerals and botanicals, have the potential to improve ageing skin. Preliminary research suggests that most of the ingredients discussed here do have properties that theoretically could benefit human skin as it undergoes environmental and chronological ageing. Whether these activities can lead to objective clinical improvement remains largely unaddressed. Further, rigorous studies that can withstand critical review are still lacking in this field, as most of the studies reviewed here are either small in scale, *in vitro* or utilize non-human models.

More research is clearly needed as no ingredient reviewed here has been the subject of a large, double-blinded clinical study. However, there are barriers to large-scale, peer-reviewed studies. Paradoxically, the cosmetics industry is not the likely leader of research in this field, as companies are usually not motivated to conduct or publish research because the nature of the trade requires secrecy regarding formulations, and because expensive trials do not always support appealing claims. Moreover, there may be no financial enticement in developing products that are found naturally and have no patent potential.

Vitamin E, vitamin C and green tea extracts represent some of the better documented, and thus more promising, over-the-counter 'natural' ingredients reviewed here. But even with these antioxidants, there is no consensus on the proper formulation or delivery vehicle. The importance of active vs. inactive forms, appropriate concentrations, consistent delivery and product stability remain hurdles which most of the published literature has yet to cross.

Although scepticism about over-the-counter cosmetic ingredients is sometimes well founded, physicians, such as dermatologists and cosmetic surgeons, should not ignore these very popular skincare products. The cosmetic effects of ageing will always remain an important issue for patients, and educating them about what has or has not been scientifically established is an important role for healthcare professionals. Additionally, interest and pursuit of further education on these ingredients, and cosmetic products in general, may ultimately drive future research that will

distinguish truly efficacious ingredients from misleading claims.

Tables

Table 1. Other popular 'natural' ingredients for ageing skin without published studies in a Medline search

Ingredient	Proposed mechanism
Seaweed extract	Antioxidant activity
Peppermint extract	Promotes circulation and relieves swelling
Algae extract	Unclear, possible antioxidant activity
Cucumber extract	Relieves swelling, suggested anti-inflammatory effects
Aloe vera	Anti-inflammatory effects
Wheat protein	Unclear
Witch hazel	Anti-inflammatory effects
Penthanol	Humectant

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