Original Contribution

Top 10 botanical ingredients in 2010 anti-aging creams

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Summary

New developments in the realm of skin rejuvenation such as phytotherapy are at an astounding increasing pace in the cosmeceutical market. Yet, many of these products that are classified as cosmeceuticals are tested less vigorously and do not have to be approved by the Food and Drug Administration to establish efficacy and safety. Thus, as clinicians, we must ask the question, ''Is there science-based evidence to validate the mechanism of these new treatments?'' We assessed the top anti-aging creams currently on the market specifically evaluating their botanical ingredients. Some of the most common botanicals that are hot off the market are: *Rosmarinus officinalis*, *Vitis vinifera* (grape seed extract), Citronellol, Limonene, *Oenothera biennis* (evening primrose), *Glycyrrhiza glabra* (licorice extract), *Aframomum angustifolium* seed extract, Diosgenin (wild yam), N6 furfuryladenine (kinetin), and Ergothioneine. Through researching each of these botanical ingredients, we have concluded that randomized controlled trials are still needed in this area, but there is promise in some of these ingredients and science to validate them.

Keywords: antioxidant, anti-aging, botanical, cosmeceutical, cosmetic dermatology, topical anti-aging

Rosmarinus officinalis

Rosmarinus officinalis, a member of the family Lamiaceae, is a very common shrub that grows wildly along the north and south coasts of the Mediterranean Sea and also in the sub-Himalayan areas.[1] It has been an important spice and medicinal herb since early times, and it has received increasing attention owing to its antimicrobial,[1–6] antimycotic,[1,6,7] antiviral,[8] anti-inflammatory,[9–11] anti-mutagen,[1,13–20] and antioxidative effects.[1,6,7,12,21–31] Thus, it is being evaluated for many disorders thought to be owing to overproduction of free radicals and lipid peroxidation such as cardiovascular diseases, diabetes, ischemia–reperfusion injury, coronary atherosclerosis, Alzheimer disease, and cancerogenesis, as well as the aging process.[1,6] Because of its diverse potential treatments, it is no surprise that it has been studied with great interest.

The antioxidant activity of plant extracts is mainly attributable to phenolic compounds. These are categorized into three groups in rosemary extracts: phenolic diterpenes possessing an abietic acid framework, flavonoids, and phenolic acids.[1,6] Carnosic acid and carnosol, abietane-type diterpenes, caffeic acid and its derivative, and rosmarinic acid are the main antioxidant compounds present in rosemary.[7,23] Del Bano *et al.* (2003) studied the antioxidant activity of six rosemary extracts with different polyphenolic compositions and proposed that they are excellent antioxidants in both aqueous and lipid systems.[30] It is generally assumed that these extracts act as free-radical scavengers but additionally may play a role by regulating apoptosis, tumor promotion, intracellular signal transduction or xenobiotic-metabolizing enzymes in the liver.[24] In one study, the diterpenes and genkwanin (a flavonoid component of rosemary) showed membrane-rigidifying effects, which may contribute to their

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antioxidant capacity through hindering diffusion of free radicals.[31]

Rosmarinic acid has been recently investigated for its ability to protect against skin tumorigenesis and DNA damage specifically by lipid peroxidation and preventing carcinogen–DNA adduct formation.[1] Carnosol has shown a number of *in vitro* and *in vivo* biological activities including strong antioxidant activity by nitric oxide inhibition assay,[21,22] anti-mutagenic effects in the Ames assay,[16] inhibition of DNA adduct formation in human bronchial cells,[17] *in vitro* anti-metastasis in B16/F10 mouse melanoma cells,[20] antiproliferative property on several human cancer cell lines and its antioxidant and anti-inflammatory properties *in vitro* in a mouse cell line[12] and *in vivo* inhibition of tumorigenesis in rodent skin,[14,15] mammary,[18] and gut models.[12,19] These results suggest that rosemary does have pharmacological effects for cancer chemoprevention and therapy.

One study specifically studied rosemary and its application in cosmetic dermatology. Calabrese *et al.* concluded that a new compound isolated from the hydrophilic fraction of a 50% aqueous methanol extract of rosemary leaves, named Rosm1, endowed strong antioxidant activity and is capable of inhibiting free radical-mediated reactions and stress-induced skin damage. They revealed this by *in vitro* tests of inhibition of reduction of cytochrome c or nitroblue tetrazolium, as well as by analysis of the susceptibility of linoleic acid to peroxidative breakdown. It showed strong antioxidant activity similar to vitamin E. This antioxidant activity was also observed *in vivo* either by exposing skin surface lipids to oxidative stress, performed in the absence and presence of added antioxidants, or after topical application of this compound to the skin of healthy human volunteers, whose surface lipids were analyzed for resistance to oxidative stress.[28]

Another study demonstrated that a water-soluble extract of *R. officinalis* could inhibit ultraviolet (UV)-induced matrix metalloproteinase-1 (MMP-1). As we know, photodamaged skin has been shown to result from both a decrease in collagen type I synthesis and its excessive degradation through the action of MMPs. This study demonstrated that *R. officinalis* extract treatment could interfere and reduce this process, thus limiting the development of photodamaged skin.[32]

As far as negative consequences of rosemary, there have been a handful of documented case reports of allergic contact dermatitis.[33–39] Otherwise, rosemary has proven to be safe in both human and animal studies. Overall, there appears to be a good deal of research validating the antioxidative effects of rosemary used systemically, but further research is needed, particularly in the role as a topical anti-aging formulation.

V. vinifera (grape seed extract)

V. Vinifera (grape seed extract) is also a flavonoid found to have antioxidative properties.[40–50] The seeds of the grape are a particularly rich source of proanthocyanidins. Grape seed proanthocyanidins (GSPs) have been shown to be potent antioxidants and free radical scavengers, being more effective than either ascorbic acid or vitamin E. Additionally, GSPs have been shown to have anti-carcinogenic activity in different cancer models.[40] They have also been shown to be protective in mice against chemical and photocarinogenesis when taken orally or applied topically.[41]

In addition to GSPs, the cis- and trans-resveratrol (a natural component of *V. vinifera* that is abundant in the skin of grapes and in the leaf epidermis and in wines) has been proven through *in vitro*, *ex vivo*, and *in vivo* experiments with yeasts, worms, flies, fish, and rodents to have antioxidative, anti-inflammatory, and anti-carcinogenic properties. Some of these activities have been implicated in the cardiovascular protective effects attributed to t-resveratrol (t-RESV) and to red wine. T-RESV has also been found to be effective in delaying the onset of a variety of age-related disease in rodents, and further research is underway on its potential role as an anti-aging agent.[42,43] All of these studies show promise, but the question remains whether they produce the same results in humans.

In 2007, Cornacchione *et al.* conducted a comparative, randomized single-blinded study where they evaluated the antioxidant properties of a *V. vinifera* shoot extract in combination with a biotechnological extract (*Ronacare hydroine*) and evaluated the efficacy on photoaging skin in humans. *In vitro*, the *V. vinifera* shoot extract appeared to have significantly stronger antioxidant capacity than vitamin C or vitamin E on keratinocytes after H_2O_2 exposure. In the same vehicle (placebo emulsion), ascorbic acid (0.5%), sarmentine (1% equivalent to 0.045% *V. vinifera* shoot extract), and the sarmentine (1%) plus *R. hydroine* (1%) combination had a significant *in vivo* antioxidant effect versus a nontreated area. The combination sarmentine (1%) plus *R. hydroine* (1%) showed a higher efficacy than sarmentine alone. The dermatologic evaluation showed that a 4-week twice-daily application of a serum containing the combination improved the main clinical signs of photoaged skin.[44] The patent is currently pending on this combination serum.

Citronellol

Citronellol, or dihydrogeraniol, is a natural acyclic monoterpenoid, which has a rose-like odor. It is a major constituent of geranium oil (approximately 30%) and rose oil (approximately 25%).[51] It is used in perfumes, shampoos, creams, and insect repellents,[52] and as a mite attractant.[53] The United Kingdom labeled it the third most frequently labeled fragrance.[54] Citronellol has caused allergic contact dermatitis so should be avoided by people with perfume allergy.[55–62] In a 2001 worldwide multicentre study on 178 patients with proven sensitization to fragrances, citronellol (5% pet) was positive in 5.6%.[55] In 2005, a six-center European and Scandinavian study of consecutively patch-tested patients found positive reactions to citronellol (0.5% pet) in 0.12%.[61] Patients with chronic hand eczema had positive reactions to citronellol (5% pet) in 0.3% of patients.[62] As a result of this, the Europeans presented a new six-ingredient fragrance mix (fragrance mix II [FM II]) for patch testing, which includes citronellol 0.5%.

Other data, such as those found by local lymph node assay, indicate little risk of allergenicity and consider citronellol as an extremely weak allergen.[63] And more recently, *in vitro* skin penetration of radiolabeled citronellol was studied under occlusion in human cadaver skin using flow-through diffusion cells and showed that citronellol had low potentials for skin penetration, which has implications on its ability to induce allergenicity.[51]

Overall, citronellol will improve the smell of your anti-aging cream and could potentially cause an allergic contact dermatitis, but it has not been proven to have any anti-aging properties.

Limonene

Limonene is one of the most inexpensive perfume ingredients. It occurs in its racemic form as dipentene, a mixture of R-limonene and S-limonene. Both isomers occur in varying proportions in several plants, including essential herb oils (rosemary, eucalyptus, lavender, caraway, lemon grass, and peppermint), tea tree oil, and turpentine oil.[62,63] R-limonene is the main constituent (98%) of peel oil from citrus fruits.[63] Limonene is common in cosmetic products and is also increasingly being used as solvents and as industrial degreasing agents and cleansers. It autoxidizes on air exposure so its pure compounds are not allergenic but their oxidation products can cause an allergic contact dermatitis. Studies have shown similar oxidation patterns and frequencies of positive patch test reactions to oxidized R-limonene and S-limonene in consecutively tested patients with dermatitis.[63] Restricting the exposure to air, reducing the recommended shelf life, and potentially adding an antioxidant to keep the peroxide concentration below 20 mM may help reduce the frequency of allergy to limonene.[54] There was no research to show that limonene causes any anti-aging effects. Generally, this botanical may make the cream smell better, but if allowed to oxidize, it can cause an allergic contact dermatitis.

Oenothera biennis (evening primrose)

Evening primrose oil (EPO) contains large amounts of gamma linoleic acid (GLA). Shafer and Kragballe have shown that oral GLA can change the lipid content of the skin in patients with atopic dermatitis.[64] A meta-analysis of nine different placebo-controlled trials performed in patients with atopic dermatitis suggested a 25% greater efficacy for GLA compared with placebo.[65] A similar randomized control trial of 12 patients found that patients treated with oral EPO compared to placebo showed a subjective improvement of skin scaling, dryness, redness, and itching.[66] Yoon *et al.* in 2001 found that EPO did have a therapeutic effect in eczematous patients and that it may be attributable to the normalization of serum gamma-interferon levels.[67] However, a parallel group study of patients with eczema and another study on chronic hand dermatitis both failed to show any improvement with EPO treatment.[68,69] Overall, it seems that the impact of oral EPO in the treatment of atopic dermatitis is marginal.[69]

Antioxidant and anti-inflammatory effects, and promising natural treatments for scleroderma and the associated Raynaud's phenomenon by EPO have also been demonstrated.[70–72]

In addition, topical application of EPO has also been studied. EPO was confirmed to effectively penetrate the skin and modulate its cell kinetic profile.[73] It proved to have a stabilizing effect on the stratum corneum barrier, but this was apparent only with the water-in-oil emulsion, not the amphiphilic emulsion. Thus, the choice of vehicle is a very important factor in the efficacy of topically applied evening primrose oil.[74] Another study where topical fish oil and EPO were topically applied to mice suggested that they both can inhibit papilloma formation, which was thought to be attributed to their ability to prevent benzo(a)pyrene binding to skin cell DNA and by enhancing the formation of lipid peroxides.[75]

In summary, EPO appears to penetrate the skin and be a fairly decent moisturizer for eczema patients, but more

studies are needed to determine its potential antioxidant effects.

Glycyrrhiza glabra (licorice extract)

Licorice is the root of *G. glabra* from which a sweet flavor can be extracted. The licorice plant is a legume, native to southern Europe and parts of Asia. The licorice extract (LE) is the safest pigment-lightening agent with the fewest side effects.[76] Thus, it is a commonly added ingredient in cosmetics for brightening the skin. Additionally, the LE has topical anti-inflammatory properties theoretically helpful in decreasing skin redness and postinflammatory hyperpigmentation. The main ingredient in the hydrophobic fraction of LE is glabridin, which inhibits tyrosinase activity in cultured B16 murine melanoma cells without affecting DNA synthesis.[77,78] Glabrene, isoliquiritigenin licuraside, isoliquiritin, and licochalcone A are other active compounds within LE shown to inhibit tyrosinase activity. Liquiritin is another main active ingredient of LE, and it appears to induce skin lightening by dispersing melanin. To see clinical results in melasma, studies demonstrated using 20% liquiritin cream applied at 1 g per day for 4 weeks.[79] It is expensive and thus used modestly in cosmetics. LE can also be considered as an effective agent for the treatment of atopic dermatitis.[80]

Predominantly, no data showed LE to decrease wrinkles, but it does appear to be more useful for the hyperpigmentation associated with photoaged skin.

Aframomum angustifolium seed extract

Aframomum angustifolium is a flowering plant whose seed extract has been shown to have anti-aging properties. One study evaluated the anti-aging effect of a natural mixture of *Aframomum angustifolium* seed extract (AASE) containing labdane diterpenoids on normal human keratinocytes or on normal human fibroblasts using low-density DNA chips. It was found to regulate antioxidant defenses, dermal–epidermal junction components, and epidermal renewal-related genes. Thus, it presented both protective and curative skin anti-aging effects.[81]

A similar study also developed a low-density DNA chip method that allowed the study of the transcriptional effect of AASE, and it too demonstrated the anti-aging properties. This same group also showed the anti-aging efficacy of a facial skin care product containing AASE through an *in vivo* single-center study using image processing analysis. The data obtained in their two-center study suggested that the AASE cream produced a global rejuvenation effect in terms of redness, pigmentation, and fine lines similar to that noted utilizing an intense pulse light source. Twenty-eight percent of the subjects reported a <50% overall global improvement in their skin by the end of the study compared to 11% of the subjects after 4 weeks of treatment. Seventy-six percent of subjects said they would purchase the cream.[82]

Most importantly, AASE does have some science-based medicine to help validate its use in anti-aging creams.

Diosgenin (wild yam)

Diosgenin is extracted from the root of wild yam (*Dioscorea composita* or *Dioscorea villosa*). It is a steroid found in a variety of plants. Traditionally, it has been used to treat diabetes, hypercholesterolemia, and gastrointestinal ailments. It is structurally similar to endogenous estrogen (E2) and displays anti-inflammatory effects as E2. The decline of E2 levels is associated with a variety of cutaneous changes owing to skin aging, and many of these changes can be improved or reversed by supplementation with estrogens. Thus, diosgenin might have the same efficacy against anti-aging. In one study, they examined the effect of diosgenin on keratinocyte proliferation and skin thickness. They found that diosgenin restored keratinocyte proliferation *in vitro* and oral administration of diosgenin improved the reduced skin thickness in ovariectomized mice. In addition, diosgenin given orally did not increase tumor growth in breast cancer–burdened mice as it did with E2.[83] Root extract has been concluded to be safe for use in cosmetic formulations.[84] However, there is not currently any clinically based trials using such a topical formulation for anti-aging, so more research is needed.

N6 furfuryladenine (kinetin)

Kinetin is a cytokinin plant hormone that has growth-promoting and anti-aging effects on plants. Initially, kinetin was shown to delay the onset of several characteristics of aging in human fibroblast culture.[85] Then, it was given orally to fruit flies, which prolonged their lifespan and slowed aging.[86,87] From there, it has been reported to have antioxidant properties[88–92] and has been identified as a naturally occurring base modification of DNA.[91,92]

Kimura *et al.* in 2004 revealed that topical treatment with kinetin normalized hyperpigmentation and improved the aged skin structure of hairless dogs without

any adverse effects.[93] McCullough and Weinstein published the first human data showing improvement in skin texture, color, blotchiness, and fine wrinkles after 24 weeks of twice-daily topical application of kinetin. There was also a 26% increase in barrier function (transepidermal water loss inhibition) at 24 weeks.[94] In an *in vitro* study, kinetin alone influenced keratinocyte proliferation and differentiation as well as formation of basement membrane and elastic network in the upper dermis.[95] In 2007, a randomized, double-blinded, placebo controlled, split-face comparative trial compared topical kinetin combined with niacinamide *vs*. niacinamide alone *vs*. vehicle placebo in an Asian cohort. Their results demonstrated that kinetin and niacinamide exerted a synergistic anti-aging effect.[88]

In contrast, another study demonstrated that ubiquinone, idebenone, and kinetin provided ineffective photoprotection to the skin compared to a topical antioxidant combination of vitamins C and E with ferulic acid.[96]

Rosacea was also treated with kinetin in a small case series. It demonstrated that topical kinetin 0.1% solution was beneficial in reducing erythema and overall clinical scores in mild to moderate rosacea. It was also well tolerated and improved the skin texture and mottled hyperpigmentation.[97] Keep in mind, these patients were also given a daily sunscreen to wear, which by itself can also help to improve rosacea.

Mostly, kinetin does appear to have some anti-aging properties, but further larger studies are needed to compare it to the other antioxidants and sunscreens.

Ergothioneine

Ergothioneine (EGT) is an antioxidant amino acid that humans consume with plant food such as corn, oats, and other grains. It is a very potent antioxidant[98–103] without taste or smell because of its unusual thione group.[98] It is found most prominently in organs or cells where oxidative stress is high, such as erythrocytes, liver, and kidney. It was found to be a more powerful antioxidant than either coenzyme Q10 or idebenone because of its relatively greater efficiency in directly scavenging free radicals and in protecting cells from ultraviolet-induced reactive oxygen species (ROS).[101] It was also demonstrated to suppress tumor necrosis factor-alpha (TNF-α) and MMP-1 expression. It is well known that ROS, TNF-α, and MMP-1 play important roles in UV-induced skin aging, particularly rhytid formation, so it is not surprising that EGT has been used in cosmetics.[99] In addition to anti-aging creams, it has been used in a hydroquinone cream formulation for its antioxidant and skin calming effects.[100]

Unlike other antioxidants, EGT is cell membrane impermeable and requires a specific carrier to be internalized. Thus, its protective function is restricted to cells that express the EGT receptor/transporter, OCTN1. A recent study demonstrated that EGT is accumulated in the epidermis and the epidermal keratinocytes and serves to protect them from solar-simulated UV damage by decreasing the levels of ROS, maintaining cell vitality and eliminating the need for a massive apoptotic response.[101] Thus, EGT and its receptor may represent an integral component of the skin's antioxidant defense system.

We discussed 10 of the most commonly used botanical ingredients currently in over-the-counter anti-aging creams. There are not many randomized double-blinded statistically significant studies to confirm the ''anti-aging'' properties of these ingredients, but there are some biochemical studies proving their antioxidative nature. Thus, it is difficult to assess whether these truly have any benefit over the known anti-aging effects of using sunscreens and retinoids. However, in this era, the cosmetic patients are being led toward these more natural marketed ''anti-aging'' products so it is important to be aware of them, their proposed mechanisms, and any potential consequences.

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