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Current Concepts in the Treatment of Recurrent Aphthous Stomatitis

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ABSTRACT

The treatment of recurrent aphthous stomatitis (RAS) still remains nonspecific and is based primarily on empirical data. The goals of therapy include the management of pain and functional impairment by suppressing inflammatory responses, as well as reducing the frequency of recurrences or avoiding the onset of new aphthae. For common forms of RAS, standard topical treatment options that provide symptomatic relief include analgesics, anesthetics, antiseptics, anti-inflammatory agents, steroids, sucralfate, tetracycline suspension, and silver nitrate. Dietary modifications may also support therapeutic measures. In resistant cases of benign aphthosis or aphthosis with systemic involvement, appropriate systemic treatment can be selected from a wide spectrum of immunomodulators that include colchicine, prednisolone, cyclosporine A, interferon-α, tumor necrosis factor-α antagonists, antimetabolites, and alkylating agents.

Keywords: Recurrent aphthous stomatitis, RAS

Idiopathic aphthae are the most frequently occurring inflammatory lesions of the oral mucous membrane. Nosologically, the condition is clearly defined, but the sores are often difficult to differentiate from heterogeneously similar aphthoid ulcerations and mucosal erosions. Episodic aphthous attacks are characterized by painful lesions that range from the size of a pinhead up to several centimeters. Fibrin covered ulcerations with a hyperemic halo are typically visible on the oral mucous membrane, but they rarely appear in the genital region. Spontaneous healing is possible after many years.

Common simple aphthae, with 3-6 attacks per year, heal rapidly, are not very painful, and are restricted to the oral mucosa. They can be differentiated from complex aphthae (less than 5% of aphthosis cases), which are recurrent, present with few to unusual multiple lesions, are extremely painful, heal slowly, and can also occur in the genital region.[1] Complex aphthosis requires the accurate diagnosis of a possible causal or associated condition, such as anemia, cyclic neutropenia, folic acid or iron deficiency, ulcus vulvae acutum, aphthous-like ulcerations in HIV positive patients, gastrointestinal diseases, such as Crohn's disease and ulcerative colitis, and Adamantiades-Behçet Disease (ABD). In ABD, which represents a malignant form of aphthosis, there is an increase in both the frequency of occurrence and severity of lesions. The diagnosis of ABD is based on several clinical criteria sets, of which the International Study Group Criteria[2] are the most frequently used and the New International Criteria are the most recent.[3]

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Topical Therapy

Dietary and General Measures

Certain foods should be avoided as they appear to trigger the eruption of new aphthae and prolong the course of the lesions (e.g., foods that are hard, acidic, salty, or spicy, as well as nuts, chocolate, citrus fruits, and alcoholic or carbonated beverages). In addition, because surfactants and detergents can cause irritation, dental care products containing sodium lauryl sulphate should be avoided.[4]

Local Anesthetics

Pain relief can be attained using topical lidocaine 2% gel or spray, polidocanol adhesive dental paste, or benzocaine lozenges. Available combination preparations include a pump spray with tetracaine and polidocanol, and a mouth rinse solution that uses benzocaine and cetylpyridinium chloride as the active ingredients. As well, anesthetic-containing solutions, e.g., a viscous lidocaine 2% solution, can be applied carefully on the lesions.

Antiseptic and Anti-inflammatory Therapies

Mouth washes with ingredients known to mildly inhibit inflammation can be used, e.g., chamomile extract solution (Kamillosan®, MEDA Pharma). Research has shown that the use of chlorhexidine (CHX) mouth rinses on RAS may be particularly helpful.[5] Other dosing forms of CHX include dental gels or throat sprays. Triclosan is a broad spectrum antibacterial agent that also exhibits antiseptic, anti-inflammatory, and analgesic effects. Available formulations include toothpastes and mouthrinses. A randomized, double-blind study that explored the topical application of diclofenac 3% in hyaluronan 2.5% reported a significant reduction in pain.[6] For adjuvant therapy, dexpanthenol, which acts as an humectant, emollient, and moisturizer, can be used in different application forms and is available without prescription.

Local Cauterization

Applications of hydrogen peroxide 0.5% solution, silver nitrate 1%-2% solution, or a silver nitrate caustic stick represent several older therapeutic methods that can reduce the duration of solitary aphthae. Cauterizing chemical treatments must be administered by a dentist or physician to avoid burning healthy tissues.

Tetracycline

Localized therapy with tetracycline can effectively reduce the duration and pain of oral aphthae.[7] To avoid difficulties related to the chemical stability of tetracycline when it is formulated in an aqueous solution, a prescription for compounding and preparation, as shown in Table 1, has been proposed.[8] Due to acidic pH values, patients may experience a brief burning sensation, but contact sensitization has not been reported in the context of intra-oral topical tetracycline applications. Marked improvement has been described with the use of a dental paste containing chlortetracycline 3%.[9]

Sucralfate

Topical sucralfate is effective in treating RAS ulcerations when administered at 5mL, 4 times/day. Sucralfate exerts a soothing effect on lesions by adhering to mucous membrane tissues and forming a protective barrier on the affected site. This drug is commonly used to treat peptic ulcers.

Topical Steroids

Topical steroids, such as triamcinolone acetonide and prednisolone (2 times/day), are formulated as oral pastes, and are commonly used in the management of RAS. Additionally, therapeutic benefit can be derived from a mouthwash containing betamethasone. Of concern is the fact

Tetracycline Mouth Wash 5%

Composition:
Tetracycline hydrochloride 5.0gm
Methyl-4-hydroxybenzoate 0.1gm
Sodium citrate 6.5gm
Propylene glycol 0.6gm
Sorbitol solution 70% (noncrystalizable) 65.5gm
Traganth 0.5gm
Purified water to 118.2gm

Preparation:
- Dissolve 4-methyl hydroxybenzoate in propylene glycol.
- Dissolve sodium citrate in purified water.
- Mix dry traganth and tetracycline hydrochloride. Mix with an equal part of sorbitol solution and form a gel with the rest of the sorbitol solution.
- Add the sodium citrate solution in portions and stir.
- Add the propylene glycol together with the dissolved methyl-4-hydroxybenzoate and stir.

Expiration: after 6 months

Instructions for Use
Shake before each use. Apply 5mL of the suspension solution for 5 minutes in the mouth cavity up to 5 times daily. For intensive therapy, the same dose should be held for 10-15 minutes in the mouth.

Box 1 Preparation and use of chemically stable tetracycline suspension. Adapted from the New German Pharmacopoeia for compounded medication: Rezepturhinweise: Tetracyclinhydrochlorid in zahnärztlichen Anwendungen und Mundspülungen.[8]

that the long-term use of steroids may predispose patients to developing local candidiasis. Combination therapy with a topical anesthetic during the day and a steroid paste at night is widely accepted as the optimal treatment regimen. An intralesional injection of triamcinolone (0.1-0.5mL per lesion) can be considered for painful single aphthae. For the treatment of genital aphthous ulcers, a combination of fluorinated steroids and antiseptics that are formulated in a cream base can be effective (e.g., dexamethasone 0.1% + chlorhexidine 1% or flumetasone 0.02% + clioquinol 3%).

New Findings

Application of 5-aminosalicylic acid 5% cream (applying a small amount to cover the aphthae 3 times/day), or a toothpaste containing amyloglucosidase and glucose oxidase can reduce pain and lessen the duration of oral aphthae.[10] A topical prostaglandin E2 gel prevented the appearance of new aphthae in a short-term study involving a small number of patients.[11] According to the experience of several patients, raw egg white may partially soften oral pain in RAS. Interestingly, the number of aphthae and frequency of recurrence are reduced during phases of smoking compared with phases of abstinence; experimental data confirmed the anti-inflammatory effect of nicotine and biochanin A on keratinocytes.[12,13] Also, a small study showed the remission of aphthosis during therapy with chewable nicotine tablets.[14]

Systemic Therapy

Colchicine

Colchicine has been shown to reduce the number and duration of lesions in up to 63% of patients with RAS.[15] Treatment over 6 weeks, followed by long-term (years) therapy (1-2mg/day) is recommended. However, relapse following treatment discontinuation is common. Physicians must ensure that appropriate contraceptive methods are practiced by patients before initiating treatment. From our experience, combination therapy with colchicine and pentoxifylline, benzathine penicillin, immunosuppressants, or interferon-alpha (IFN-α) is possible.

Pentoxifylline

In uncontrolled studies, pentoxifylline (300mg, 1-3 times/day) was shown to be effective against orogenital aphthae. The response rates in children ranged between 36% and 63%.[16]

Corticosteroids

Systemic corticosteroids are used as rescue treatment in patients with acute exacerbation and in those who inadequately responded to therapy with colchicine and pentoxifylline. Oral prednisolone, or its equivalent, at 10-30mg/day for up to 1 month can be administered during an outbreak. From our experience, intravenous (IV) pulse therapy at 100mg/day for 3 days results in quick improvement for severe cases of RAS without the side-effects that are associated with long-term prednisolone use. Patient surveillance during therapy is advisable.

Dapsone

Dapsone (100mg/day) can be used for oral and genital aphthae, however, rapid relapses can occur after discontinuation of treatment. Intermittent administration of ascorbic acid and the reduction of smoking are useful in averting hematologic side-effects.[17]

Thalidomide

Under standard (100-300mg/day) or low (50mg/day) dosing levels of thalidomide, a dose-dependent effect against orogenital ulcerations emerges within 7-10 weeks following treatment. Due to teratogenicity and other potentially severe side-effects, therapy should be reserved for exceptional cases, such as in patients with persistent peripheral neuropathy.

Antimetabolites (Azathioprine and Methotrexate)

Azathioprine (Imuran®, GlaxoSmithKline) at 50-150mg/day can reduce the frequency and extent of severe orogenital aphthosis in ABD, as demonstrated in placebo-controlled studies.[18] It is contraindicated for women who are pregnant or breastfeeding, and it is not recommended for use in pediatric patients. During treatment, blood cell count and liver function should be monitored. Methotrexate (7.5-20mg/week) has been proven to be effective in severe orogenital aphthosis. While on therapy, folic acid should be administered intermittently.

Cyclosporine A

Cyclosporine A, at a dosage of 3-6mg/kg, was shown to be effective in about 50% of ABD patients with respect to aphthosis.[19] However, abrupt withdrawal of therapy may lead to a rebound phenomenon. Due to the potential for severe side-effects from therapy, clinical and serologic vigilance must be observed.

Interferon-alpha (IFN-α)

Recombinant IFN-α preparations, IFN-α 2a and 2b, have not been tried for RAS; however, they have successfully treated ABD. A study evaluating the efficacy and safety of systemic IFN-α in patients with ABD reported complete or partial remission of mucocutaneous lesions.[20] Intermediate or high doses of IFN-α 2a (6-9 x 10^6 units, 3 times/week) seemed to be more effective than the low dose (3 x 10^6 units 3 times/week). The low dose may be recommended for maintenance therapy if the treatment is shown to be effective within 1-4 months. Disease recurrences after stopping IFN therapy were common, but reinstatement of therapy also elicited a rapid response.

Biologics

Infliximab (Remicade®, Centocor) at 5mg/kg IV can be administered at different time intervals. As early as several days following the first dose, rapid healing can occur, even in patients with refractory recurrent disease who exhibit both oral and genital ulcers. It is possible that relapses may not occur within the first 6 weeks of starting therapy. Etanercept (Enbrel®, Amgen-Wyeth) at 25mg, twice weekly,

given subcutaneously) appears to be effective on oral, but not on genital aphthae.[21]

Alkylating Agents

Monotherapy with chlorambucil on orogenital ulcerations in ABD demonstrated a good response when administered at an initial dose of 0.1mg/kg, followed by a low maintenance dose of 2mg/day.[22] Orogenital aphthae in ABD patients also improved when using pulse therapy combined with cyclophosphamide. Treatment with alkylating agents should be limited exclusively to patients with severe forms of systemic aphthosis.[22]

Other Systemic Therapies

In a study involving 13 patients, minocycline (100mg/day) was found to be effective in genital aphthosis, but it was ineffective against oral aphthosis.[23] For the immunomodulator, levamisole, treatment at 150mg/day on 3 consecutive days/week during attacks has been occasionally reported to be effective against orogenital aphthae.[24,25] Subcutaneous testosterone, administered once yearly, was shown to be effective in individual female patients who developed aphthae premenses.[26] Also, oral contraceptives containing high levels of estrogen can be used successfully; improvement may be expected after 3-6 months.

Conclusion

Localized topical regimens are considered to be the standard treatment in mild cases of RAS. In more severe cases, topical therapies are likewise very useful in reducing the healing time, but they are often ineffective at prolonging disease-free intervals. For most patients with RAS, monotherapy with colchicine, or in combination with either pentoxifylline or the short-term use of prednisolone, is satisfactory. Furthermore, highly efficacious drugs from a wide spectrum of immunomodulatory agents are available. However, they should not be utilized without first cautiously weighing the risks and the benefits for each patient.

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Antioxidants Used in Skin Care Formulations

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ABSTRACT

The formation of free radicals is a widely accepted pivotal mechanism leading to skin aging. Free radicals are highly reactive molecules with unpaired electrons that can directly damage various cellular structural membranes, lipids, proteins, and DNA. The damaging effects of these reactive oxygen species are induced internally during normal metabolism and externally through various oxidative stresses. The production of free radicals increases with age, while the endogenous defense mechanisms that counter them decrease. This imbalance leads to the progressive damage of cellular structures, and thus, results in accelerated aging. Antioxidants are substances that can provide protection from endogenous and exogenous oxidative stresses by scavenging free radicals. Topical antioxidants are available in multivariate combinations through over-the-counter skin care products that are aimed at preventing the clinical signs of photoaging.

Key Words: antioxidants, photoaging, topical treatments, skin aging

Skin aging is a complex process involving various genetic, environmental, and hormonal mechanisms. One can differentiate between intrinsic, chronologic aging and extrinsic, "environmental" aging; both processes occur in conjunction with the other and are superimposed on each other. Free radicals play a central role in the course of both intrinsic and extrinsic aging. During the chronologic aging process, free radicals are formed naturally through normal human metabolism, whereas, in the extrinsic aging process, they are produced by exogenous factors, such as UV exposure, cigarette smoking, and alcohol consumption. At least 50% of UV-induced damage to the skin is estimated to be attributable to the UV-induced formation of free radicals.[1] Harman, et al. first proposed this "free radical theory of aging" in 1956, and today it is one of the most widely accepted theories used to explain the cause of aging.[2]

Free radicals are highly reactive molecules with an odd number of electrons that are generated from oxygen;[3] they can damage various cellular structures, such as DNA, proteins, and cellular membranes. In addition, free radicals may lead to inflammation, which seems to play an additional role in skin aging.[4]

The body possesses endogenous defense mechanisms, such as antioxidative enzymes (superoxide dismutase, catalase, glutathione peroxidase) and nonenzymatic antioxidative molecules (vitamin E, vitamin C, glutathione, ubiquinone), protecting it from free radicals by reducing and neutralizing them.[5] Some of these antioxidant defense mechanisms can be inhibited by ultraviolet (UV) light.[6] Moreover, as part of the natural aging process endogenous defense mechanisms decrease, while the production of reactive oxygen species increases, resulting in accelerated skin aging.

It is intuitive to hypothesize that the topical application of antioxidants may neutralize some of the resulting free radicals, and consequently lessen or prevent the signs of aging skin. At present, topical antioxidants are marketed to prevent aging and UV-induced skin damage, as well as to treat wrinkles and erythema due to inflammation (e.g., post laser resurfacing). However, currently, only vitamin C can actually treat wrinkles by influencing collagen formation through a mechanism other than antioxidation. For other products, their ability to improve wrinkles is either due to swelling or hydrating effects, or to other formulary constituents, such as retinol and vitamin C. Hence, antioxidants can prevent wrinkles, but not treat them.

For topically administered antioxidants to be effective in preventing skin aging, a couple of considerations should be made when formulating them:

- Product stabilization is crucial. Because antioxidants are very unstable, they may become oxidized and inactive before reaching the target.
- They must be properly absorbed into the skin, reach their target tissue in the active form, and remain there long enough to exert the desired effects.

Many antioxidants have been used for centuries in ancient and modern cultures around the world for various diseases.[7] In addition to their antioxidant activity, most of them possess numerous other biologic properties, e.g., they can be anticarcinogenic and anti-inflammatory. This article will discuss antioxidants that are currently marketed in cosmetic formulations and will focus on their antioxidant activities.

Vitamin E

Vitamin E (tocopherol) is a lipid-soluble antioxidant that is present in the skin and found in various foods, such as vegetables, seeds, and meat.[8] There are 8 active isoforms that are grouped into tocopherols and tocotrienols. Of the 4 tocopherols

(α-, β-, γ- and δ-), α-tocopherol (AT) has the highest activity. In animals, a topical application of α-tocopherol has been shown to exert photoprotective effects by reducing the number of sunburn cells,[9] reducing ultraviolet B (UVB)-induced damage,[10] and inhibiting photocarcinogenesis.[11] In humans, tocopherol 5%-8% cream that was applied to the face improved signs of photoaging when compared with placebo.[12] Furthermore, application of vitamin E (5%) to human skin under light-tight occlusion 24 hours before UV treatment was shown to inhibit human macrophage metalloelastase, a member of the matrix metalloproteinase family involved in the degradation of elastin.[13]

Newer studies suggest that the combined application of various antioxidants can increase their potency when compared with 1 antioxidant alone, and consequently can provide superior photoprotection, as has been shown for the combination of vitamins E and C.[14] Topical application of vitamin E has been linked with various cutaneous side-effects, including contact dermatitis.[15-17]

Coenzyme Q10

Coenzyme Q10 (CoQ10), or ubiquinone, is a fat-soluble antioxidant that is found in all human cells as a component of the respiratory chain, as well as in food, e.g., fish and shellfish. Up to 95% of the body's energy requirements seem to be provided by CoQ10.[18] *In vitro* studies showed that CoQ10 suppressed the expression of collagenase following ultraviolet A (UVA) irradiation.[19] In human skin, few studies exist on the topical effect of CoQ10. Nevertheless, CoQ10 is a popular topical antioxidant included in several over-the-counter (OTC) cosmetic products. No side-effects with topical application of CoQ10 have been reported to date.

Idebenone

The synthetic analog of coenzyme Q10 is called idebenone, which has been demonstrated to be stronger than CoQ10 and other well known antioxidants.[20] In humans, a study with a topical skin care formulation containing idebenone showed positive effects on photodamaged skin (i.e., reduction in skin roughness/dryness, reduction in fine lines/wrinkles).[21] However, the effects on wrinkles were most likely due to hydration or skin irritation. There is 1 report of contact dermatitis attributed to idebenone 0.5% in a cream.[22] However, the authors have seen many patients who developed contact dermatitis from skin care products containing idebenone.

Lycopene

Lycopene, a powerful antioxidant, is a carotenoid found in red fruits and vegetables. It is, in fact, responsible for their red color.[23] Its chemopreventive effects against photo-induced tumors have been proven in mouse models.[24] Despite very little clinical data, lycopene is included in various skin care products.

Vitamin C

In humans vitamin C (ascorbic acid) can be obtained solely from food, such as citrus fruits. Sunlight and environmental pollution can deplete vitamin C present in the epidermis[25] and because vitamin C is a potent antioxidant, enhancing its levels in the skin seems reasonable. Vitamin C predominantly exists in its reduced form, ascorbic acid. Its oxidized form, dehydro-L-ascorbic acid can be found in trace quantities and can revert back to ascorbic acid. However, if the lactone ring irreversibly opens, diketogulonic acid is formed, which is no longer active. This happens when vitamin C preparations are oxidized, rendering them ineffective and useless.[26] Thus, vitamin C preparations should be kept in airtight, light-resistant containers to avoid exposure to UV rays or the air.

Topical vitamin C as a photoprotectant has been studied *in vitro* and *in vivo*, demonstrating its effects in preventing sun damage by reducing sunburn cells and decreasing erythema when exposed to both UVA and UVB irradiation.[27] The addition of topical vitamin C to either a UVA or UVB sunscreen was shown to improve sun protection when compared with sunscreen alone.[28] Furthermore, adding topical vitamin C to "after–sun" products has been shown to scavenge UV-induced reactive oxygen species.[29]

Ascorbate is required for collagen synthesis[30] and the addition of ascorbic acid increases collagen production in human skin fibroblasts.[31] At the same time it may reduce production of elastin by an unknown mechanism.[32] Two studies in humans have shown an improvement in the appearance of wrinkles upon topical application of vitamin C.[33,34] However, more clinical trials are necessary to unravel all the effects of vitamin C on skin and aging. Thus, vitamin C preparations are useful in preventing or lessening the detrimental effects of UV radiation. Some patients experience minimal discomfort (stinging and mild irritation) from topical application.

Green Tea

Green tea is a very popular beverage as well as an antioxidant, that is extracted from the plant *Camellia sinensis*. There are 4 major polyphenolic catechins, of which Epigallocatechin 3-gallate (EGCG) is the most abundant and biologically active. The green tea polyphenols (GTP) possess not only antioxidant activity, but they also act as anti-inflammatory and anticarcinogenic agents. GTP can be administered either orally or topically.[35] With various *in vitro* and *in vivo* studies, green tea is probably the most studied antioxidant. *In vivo* topical application of GTPs has been shown to suppress chemo- and photocarcinogenesis in mice,[36] and prevent UV-induced oxidative damage and induction of matrix metalloproteinases.[37] In human skin, GTPs reduced UV-induced erythema, the number of sunburn cells, immunosuppression, and DNA-damage.[38] In spite of the limited data in humans, there are numerous OTC products containing green tea, and using them every morning for photoprotection in combination with a sunscreen makes sense. As with most of the antioxidants, no controlled

clinical trials exist and the concentration of phenols in the various products is not standardized.

Silymarin

Silymarin, derived from the milk thistle plant, *Silybum marianum*, is a natural polyphenolic flavonoid. Its main component silybin (silibinin), is considered to be the most biologically active with strong antioxidant properties.[39] *In vivo* studies have shown photoprotective effects with topically applied silybin prior to, or immediately after, UV irradiation.[40] Thus, there is reasonable evidence to include the compound into sunscreens.

CoffeeBerry®

CoffeeBerry® (VDF FutureCeuticals) is the proprietary name for an antioxidant extracted from the fruit of the coffee plant *Coffea arabica*. It has been shown to be a stronger antioxidant than green tea, pomegranate extract, vitamins C and E.[41] It contains polyphenols, which are well known for their antioxidant properties.[42] In 2007, a product containing CoffeeBerry® polyphenols 1% (Revaléskin™, Stiefel Laboratories) was launched. The company claims that its use over a 6-week period can result in significant improvement of hyperpigmentation, fine lines, wrinkles, and overall appearance. Furthermore, there have been no reports of irritation by patients with sensitive skin. However, further prospective, randomized and controlled human studies assessing the antioxidant effects of topical preparations containing CoffeeBerry® extract are needed.

Resveratrol

The antioxidant resveratrol is a polyphenolic phytoalexin compound that is found in grapes, nuts, fruits, and red wine, among others.[43] *In vitro* and *in vivo* studies have shown that, when topically applied, resveratrol protects against UVB-mediated cutaneous damage and inhibits UVB-mediated oxidative stress.[44-46] The effect of resveratrol on human skin and photoaging remains to be examined. It is included in a few products that claim to have antiaging benefits.

Grape Seed

Grape seed is extracted from *Vitis vinifera* and is rich in proanthocyanidins, which belong to the flavonoid family. Proanthocyanidins are potent antioxidants with strong free radical scavenging activities.[47] Grape seed extract has been shown to be an even stronger scavenger of free radicals than vitamins C and E.[48] A possible antioxidant mechanism of photoprotection by grape seed proanthocyanidins (GSP) was suggested by Mittal, et al.[49] GSP was shown to inhibit the depletion of antioxidant defense components induced by UVB,[50] and topical application of grape seed extract seems to enhance the sun protection factor in humans.[43] It is included in topical cosmetic formulations for antiaging purposes.

Pomegranate

Pomegranate extracts can be obtained from various parts of the fruit *Punica granatum*, such as the juice, seed, and peel. In particular, the phenolic components have potent antioxidant activity.[51] Topical application of the peel extract was shown to restore catalase, peroxidase, and superoxide dismutase enzyme activities *in vivo*.[52] The fruit extract has been shown to ameliorate UVA-mediated damages,[53] and protect against the adverse effects of UVB radiation *in vitro*.[54] Pomegranate extract is available in various skin care products.

Genistein

Genistein is an isoflavone derived from soybeans with the capacity to inhibit UV-induced oxidative DNA damage.[55] Genistein, either topically applied or orally supplemented, was shown to effectively protect human skin against UVB-induced skin photodamage.[56,57] It is included in various products such as facial moisturizers, sunscreens, and other skin care formulations that claim to provide anti-aging effects.

Pycnogenol

Pycnogenol can be extracted from the French maritime pine (*Pinus pinaster*). It contains flavonoids and phenolic compounds, which act as potent free-radical scavengers. Immunosuppression and a reduction of the inflammatory sunburn reaction were observed in mice after topical application of pycnogenol 0.05%–0.2%.[58] The potential of pycnogenol to provide photoprotection for humans has been investigated for oral supplementation, showing that a significantly elevated UV radiation level was necessary in order to reach 1 minimal erythema dose.[59]

Niacinamide

Niacinamide, or nicotinamide, is the biologically active amide of vitamin B3. Besides its antioxidant activity, it has also been shown to exhibit anti-inflammatory, depigmenting, and immunomodulant properties. The use of niacinamide has been shown to improve the texture and tone of the skin, and reduce fine lines, wrinkles, and hyperpigmentation.[60] Topical niacinamide is well tolerated and can be found in various skin care products.

Conclusion

The use of topically applied antioxidants seems promising; however, there is a paucity of controlled clinical trials in humans examining the role of antioxidants in preventing or decelerating skin aging. Thus, further experimental data needs to be generated. Current research suggests that combinations of different antioxidants seem to have synergistic effects and, thus, better efficacy, when compared with 1 antioxidant used alone.[61,62] Also, some data suggest that a cumulative or additive benefit can be derived from using oral and topical antioxidant products in combination.[63,64] In spite of the lack of data, millions of dollars are spent

annually on these products worldwide. At this point, it is important to understand that these agents are harmless when applied topically, but the exact efficacy of these products is currently unknown.

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Class	Name/Company	Approval Dates/Comments
Rheumatoid Arthritis	**Certolizumab pegol** *Cimzia®* UCB S.A.	The European Medicines Agency (EMEA) has accepted for review a Marketing Authorization Application in July 2008 for this PEGylated anti-TNFα biologic therapy for the treatment of adults with moderate-to-severe rheumatoid arthritis. This antibody has been shown to reduce the rate of joint damage progression and improve physical function. Crohn's disease is a US FDA-approved indication and development for psoriasis is currently underway.
Psoriatic Arthritis	**Golimumab** Centocor	The US FDA received a Biologics License Application in June 2008, requesting approval of this next-generation anti-TNF-α monoclonal antibody as a monthly subcutaneous treatment for adults with active forms of rheumatoid arthritis, psoriatic arthritis, and ankylosing spondylitis.
Antibacterial Agent	**Ceftobiprole medocaril** *ZEFTERA®* Basilea Pharmaceuticals	Health Canada authorized the marketing of this antibiotic in June 2008 for the treatment of complicated skin and soft tissue infections, including diabetic foot infections. Ceftobiprole is the first approved broad spectrum antimethicillin-resistant *Staphylococcus aureus* (MRSA) antibiotic belonging to the cephalosporin class.
HIV and AIDS	**Tipranavir** *Aptivus®* Boehringer-Ingelheim	The US FDA approved this oral formulation in June 2008 with dosing information for treatment-experienced pediatric patients aged 2 to 18 years who are infected with HIV-1. The recommended pediatric dose for both the capsules and oral solution is 14mg/kg with 6mg/kg ritonavir, or 375mg/m^2 tipranavir coadministered with 150mg/m^2 ritonavir. Prescribers should calculate the appropriate dose for each child based on body weight (kg) or body surface area (m^2) and should not exceed the recommended adult dose of 500mg coadministered with 200mg ritonavir twice daily.

Drug News

New Guidelines

The National Institute for Health and Clinical Excellence of the UK National Health Service published new guidelines on the use of adalimumab for the treatment of psoriasis in adults. This product is recommended as a possible treatment for adults with plaque psoriasis only if:

- their condition has not improved with other treatments, such as cyclosporin, methotrexate, and psoralen + long-wave ultraviolet radiation (PUVA).
- they have experienced side-effects with these treatments in the past
- there is a medical reason why they should not receive these treatments.

Treatment with adalimumab should only be continued beyond 16 weeks only if the psoriasis has clearly improved within this time.

The severity of a patient's psoriasis before and during treatment should be assessed by considering the redness, thickness, and scaliness of the plaques, as well as the area of the body involved, and how the condition affects the person's quality of life. When assessing a patient's psoriasis, healthcare professionals should take into account any disabilities or difficulties in communication, as poor communication may indicate that standard assessments will not provide accurate information about the patient's condition.

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