Exploration of “Alternative” and “Natural” Drugs in Dermatology

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Objective: To review some of the promising natural remedies within dermatology to explore their potential clinical benefit in supplementing conventional drugs.

Data Sources: MEDLINE searches from January 1966 through October 2000 and Science Citation Index searches from January 1974 through October 2000 were conducted.

Study Selection: Primary importance was given to in vivo and in vitro controlled studies, the results of which encourage further exploration.

Data Extraction: The controls used, the statistical approach to analysis, and the validity of the experimental method analyzed were considered particularly important. Data were independently extracted by multiple observers.

Data Synthesis: Natural remedies seem promising in treating a wide variety of dermatologic disorders, including inflammation, phototoxicity, psoriasis, atopic dermatitis, alopecia areata, and poison oak.

Conclusions: The alternative medications presented seem promising, although their true effects are unknown. Many of the presented studies do not allow deduction of clinical effects. Further experimentation must be performed to assess clinical benefit.

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Recenfly, alternative remedies have been investigated to supplement traditional drugs. We performed a literature search to highlight recently reported medicaments. Emphasis was placed on studies that followed the evidence-based dermatology guidelines.1,2

RESULTS

Alternative medications and their potential clinical uses from human studies and animal and in vitro studies3-24 are summarized in the Table.

TEA EXTRACTS

Ultraviolet solar radiation may induce a variety of adverse effects in humans, including melanoma,25 photaging of the skin,26,27 sunburn,28 and immunosuppression.29,30 Protection against UV-induced skin damage includes avoidance of sun exposure, application of sunscreens, low-fat diets,31,32 and pharmacologic intervention with retinoids.33 More recently, green tea extracts have been reported to be beneficial in treating UV-induced photodamage.

In a study by Elmets et al,4 1% to 10% green tea polyphenolic (GTP) fraction-sin ethanol and water vehicle were applied onto the backs of 6 volunteers. Thirty minutes after GTP application, patients were exposed to twice the minimal erythema dose of UV radiation from a solar simulator. The minimal erythema dose was determined for each patient by exposing skin to graded doses of UV radiation from the solar simulator. Green tea extracts resulted in a dose-dependent reduction of UV-induced erythema as measured by chromatometry and visual evaluation.

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The (-)-epigallocatechin-3-gallate and (-)-epicatechin-3-gallate polyphenolic fractions were most effective, while the (-)-epigallocatechin (EGC) and (-)-epicatechin fractions had little effect. Histologic examination showed a decrease in sunburn cells in GTP-treated skin. Epidermal Langerhans cells, the antigen-presenting cells involved in the skin immune response, were significantly protected against UV damage. Finally, GTP fractions reduced UV-induced mutations in DNA, as detected by means of a phosphorus 32 postlabeling technique. Spectrophotometric analysis indicated that GTP fractions did not absorb UV-B light, implying a mechanism of action different from the UV-A absorption of sunscreens.
from that of sunscreens. This study demonstrates the potential benefit of GTP extracts in preventing UV-induced immunosuppression and erythema.

The use of GTP extracts was also found to be beneficial in treating UV-induced immunosuppression in mice. The GTP extracts, fruits and vegetables, and quercetin and chrysin significantly prevented the UV-induced suppression of contact hypersensitivity to picryl chloride when compared with irradiated, untreated control (P<.05). Increased ear thickness measurements were used to evaluate the response. The GTP was administered in concentrations of 0.1% and 0.01%. Green tea extracts have been beneficial in preventing early signs of photochemical damage to mouse and human skin treated with psoralen–UV-A therapy. Psoralen–UV-A, a treatment for psoriasis, increases the patient’s risk of developing melanoma and squamous cell carcinoma. Pretreatment and posttreatment with the green tea extracts in mouse and human skin significantly decreased markers of this photochemical damage, namely hyperplasia and hyperkeratosis, c-fos and p53, and erythema, (P<.05), when compared with vehicle controls (water given before and after treatment). The effects of green tea on skin are further discussed by Katiyar et al.

Oral and topical standardized black tea extracts also decreased photochemical damage to the skin. In one study, standardized black tea extracts significantly reduced erythema and skinfold thickness associated with UV-B-induced carcinogenesis in cultured keratinocytes and mouse and human skin (P<.05). In topically treated mice, a 64% reduction in severity of erythema and a 50% decrease in skinfold thickness were observed when compared with vehicle control. A decrease in the expression of c-fos, c-jun, and p53 in mouse skin and keratinocytes pretreated with standardized black tea extracts was also noted. This study indicates that when green tea is oxidized to black tea, the extracts remain beneficial in preventing the early signs of UV-B–induced phototoxic effects, namely, sunburn and skin thickness.

**OTHER HERBS**

Tea produced from the leaves of the *Eucommia ulmoides* OLIVER tree (EUOL) is commonly consumed in China, Korea, and Japan. Geniposidic acid, a main component of EUOL, seems beneficial in improving some of the signs of aging in model rats. Falsely aged model rats fed a diet consisting of a 2.4% water-soluble methanol extract of EUOL had a statistically significant increased stratum corneum turnover rate compared with rats fed a comparable diet without the EUOL. In a similar experiment, rats fed geniposidic acid also had improved stratum corneum turnover. With aging, the stratum corneum turnover rate decreases, suggesting that EUOL and, specifically, geniposidic acid may alter the aging process.

Benzoyl peroxide (BPO) is a free radical–generating compound and strong oxidizer. It is commonly used as a polymerization initiator, an additive in cosmetics, and a bleaching agent for flour and cheese. Spearmint may abrogate the effects of BPO-induced tumor promotion.

In a recent study, pretreatment with spearmint (*Mentha spicata*) induced a statistically significant decrease in the BPO oxidative damage, toxic effects, and cellular hyperproliferation in adult female albino mice when compared with the BPO-treated control group. Topical spearmint extracts salvaged the levels of antioxidant enzymes glutathione peroxidase, glutathione reductase, glutathione S-transferase, and catalase that are reduced by BPO treatment alone. The BPO-elevated microsomal lipid peroxidation and hydrogen peroxide generation were significantly reduced with spearmint pretreatment. Furthermore, spearmint significantly decreased markers for cellular DNA synthesis, namely ornithine decarboxylase activity and thymidine uptake, as compared with BPO treatment alone. Analysis was performed on excised mouse skin.

**HYDROXYACIDS**

Topical β-lipohydroxyacid (β-LHA), a derivative of salicylic acid, improved some of the manifestations of aging in women by inducing a statistically significant epidermal thickening and dendrocytic hyperplasia. Both the younger and elder populations exhibited improvement, but the changes were more diverse in the older women. When compared with placebo, 6% of the young and 16% of the elderly population experienced increased filagrin layer thickness. Further studies are needed to understand the mechanism of hydroxyacid action and, thereby, their full effect on aging skin.

**ESSENTIAL FATTY ACIDS**

Patients with atopic dermatitis (AD) are thought to have a reduced rate of conversion from linoleic acid to γ-linolenic acid (GLA), dihomo-γ-linolenic acid, or arachidonic acid as compared with healthy subjects. Replacement of GLA, in the form of primrose oil or borage oil, may therefore benefit in the treatment of these patients.

In fact, more than 20 randomized controlled studies assessing the effects of GLA have been performed, with most studies indicating an improved epidermal barrier on GLA application. In one recent study, topical application of 20% evening primrose oil caused a statistically significant stabilizing effect on the epidermal barrier in patients with AD as evaluated by transepidermal water loss and stratum corneum hydration. When compared with placebo, the water-in-oil emulsion of primrose oil proved effective, whereas the amphiphilic emulsion did not, emphasizing the importance of the vehicle. In addition, borage oil, which contains a large quantity of GLA, improved pruritus, erythema, vesiculation, and oozing in atopic pa-
**Alternative Medications and Their Potential Clinical Uses**

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### Animal and In Vitro Studies

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*UVII indicates UV-induced immunosuppression; GLA, γ-linolenic acid; AD, atopic dermatitis; TEWL, transdermal water loss; LDF, laser Doppler flowmetry; ODC, ornithine decarboxylase; GA, geniposidic acid; and TNF-α, tumor necrosis factor α.

†Compared with untreated control.

‡Compared with placebo.

§Vitamin E, sodium pyruvate, membrane-stabilizing fatty acid.

| At least 1 strain of cyanobacteria had an opposite effect, increasing inflammation.

**Analysis**

Patients when compared with placebo-treated patients (P < .05). Patients were given 40 drops of borage oil twice daily for 12 weeks; dermatologists and patients visually assessed the signs.³

In contrast, 2 important studies did not observe a significant clinical effect of GLA on AD compared with placebo. In studies by Bamford et al.¹⁰ and Berth-Jones and Graham-Brown,¹¹ evening primrose oil capsules did not improve erythema, excoriation, and lichenification clinical scores, as evaluated by dermatologists and patients.

Meta-analysis of all previous randomized placebo-controlled studies indicated a significant difference between treatment and placebo groups.¹²,¹³ Critics of the meta-analysis claim that it included unpublished trials and inadequate baseline data in terms of disease severity.¹⁴ Apparent differences in response between placebo and treatment groups may result from a greater severity at baseline in subjects receiving active treatment.¹⁵,²⁰ Treatment of AD with GLA remains controversial.

**ESSENTIAL OILS**

Other essential oils have been investigated in treating IgE-mediated allergic reactions as well as alopecia areata. Mice and rats pretreated with lavender oil inhibited mast cell degranulation, indicating that the oil could inhibit im-
medium-type allergic reactions. Topical and intradermal lavender oil inhibited the ear swelling response in mice and passive cutaneous anaphylaxis in rats when compared with isotonic sodium chloride solution control treatment ($P < .05$). Peritoneal mast cells were also inhibited from releasing histamine or tumor necrosis factor $\alpha$ in vitro when lavender oil was applied. 24

Alopecia areata was treated with 7 months of aromatherapy. A mixture of thyme, rosemary, lavender, and cedarwood essential oils in jojoba and grape seed carrier oils massaged into patients’ scalps significantly improved the alopecia when compared with the carrier oils alone. The efficacy of the treatment was evaluated at initial assessment and 3 and 7 months after treatment by dermatologists’ visual scoring of photographs and a computerized analysis of traced areas of alopecia. 14 This study did not mention disease duration before aromatherapy treatment. Half of patients with recent-onset alopecia areata have remission within 1 year, which could account for the aromatherapy’s putatively beneficial results. 31

ASCORBIC ACID AND VITAMIN E

The hydrophobic ascorbic acid and lipophilic vitamin E have found increasing use in dermatologic treatment. Several studies investigated the effects of both ascorbic acid and vitamin E against oxidative stress. In mice, acute and chronic UV-B–induced photodamage was significantly decreased with intraperitoneal postadministration of magnesium-L-ascorbyl phosphate (MAP), a precursor to ascorbic acid ($P < .05$). Compared with irradiated, untreated mice, MAP-treated mice had a 60% decrease in UV-B–induced tumor formation, a 50% decrease in skin thickness, and a 55% decrease in ornithine decarboxylase, a marker for DNA synthesis. In addition, on acute exposure to UV-B irradiation, MAP prevented increases of lipid peroxidation in skin and sialic acid in serum. The MAP produced an immediate and transient increase in vitamin C in the serum, skin, and liver, indicating its conversion in those tissues. 10 The effect of topical application of MAP in reducing UV-B photodamage is unknown. The clinical significance of this study remains uncertain.

Oral ingestion of ascorbic acid (2000 mg/d) and vitamin E (1000 IU/d) reduced the sunburn reaction in human subjects. The volunteers’ threshold dose for eliciting sunburn and their cutaneous blood flow of skin irradiated with incremental UV doses were determined before and after 8 days of treatment. A statistically significant difference was observed in the median minimal erythema dose of ascorbic acid– and vitamin E–treated patients as compared with placebo-treated patients. The former minimal erythema dose increased 17%, the latter declined 14%. 9

Topical pretreatment in humans with a combination of ascorbic acid, vitamin E, and melatonin provided a statistically significant enhanced photoprotection against UV-induced erythema. Dermal blood flow, visual grade, and chromatometry measures decreased with the combined treatment, as well as with each treatment alone, when compared with placebo-treated skin. The effect of the combined treatment was more pronounced. 7

Ascorbic acid and vitamin E have also proved beneficial in treating other conditions. Nitrate tolerance decreases a developed tolerance to the vasodilatory effects of nitrate, due to both neurohormonal counterregulation and enhanced response to vasoconstrictor agonists. 52 Oral administration of two 500-mg ascorbic acid capsules daily along with glycerol trinitrate for 3 days prevented nitrate tolerance in healthy volunteers taking transdermal glycerol trinitrate. With those taking ascorbic acid, the vasodilatory and conductivity responses evoked by glycerol trinitrate were potentiated throughout the 3-day period (24.5% increase vs control), while in those taking glycerol trinitrate alone, the responses slowly declined (8.2% increase vs control). 3 This observed effect was statistically significant.

A combination of vitamin E, sodium pyruvate, and membrane-stabilizing fatty acids induced a statistically significant decrease in the lesion development, duration, and severity of genital herpes simplex virus when applied after infection to guinea pigs and mice. The combined treatment yielded a 36% decrease in lesion severity score in guinea pigs and a 33% decrease in lesion size in hairless mice when compared with no treatment. 21

MISCELLANEOUS

Quaternium-18 bentonite, an organoclay used in cosmetics to thicken or stabilize the products, has been investigated for its ability to prevent poison ivy or poison oak contact dermatitis reactions in humans. Pretreatment with 5% quaternium-18 bentonite lotion on the forearm of patients with allergic contact dermatitis to poison oak or poison ivy significantly reduced or prevented a severe reaction to urushiol, the allergic resin of both plants. Trained technicians blinded to the treated area visually evaluated the reactions. Statistical significance was found when treated test sites were compared with untreated controls. 15

Pretreatment with diluted homeopathic gels effectively decreased the inflammation caused by methyl nicotinate in humans. The vasodilatory response to methyl nicotinate was measured by laser Doppler velocimetry. This measure was significantly reduced when the skin was pretreated with Urtica urens, Apis mellifica, Belladonna, or Pulsatilla aqueous gels as compared with vehicle control. 16 It is important to note that methyl nicotinate inflammation is primarily a pharmacologic effect and has few immunologic implications, thereby minimizing the clinical significance of this study.

Capsular polysaccharides from various strains of cytophobacteria were found to have anti-inflammatory effects on adult albino male mice. Six-hour application of hydrophilic extracts of capsular polysaccharides subsequent to croton oil–induced dermatitis caused a statistically significant reduction in the mouse ear edema when compared with croton oil inflammation without treatment. Some strains were not effective, and at least 1 other strain of capsular polysaccharides significantly increased the edema after croton oil application by about 29%. The most effective inflammation-reducing strains decreased the edema by as much as 36%, were dose-dependent, and were composed primarily of neutral sugars, uronic acids, and proteins. The inflammation-increasing extract contained a monosaccharide composition (glucose and mannose) similar to those of extracts that most significantly decreased dermatitis. 23
The sampling of investigative medications presented by this review seems promising, although their true effects are unknown. Caution must be used when animal studies are interpreted. In addition, experimental design, such as sample size, drug concentration, method of exposure to the medicine, and analytic techniques, may greatly influence a study’s outcome. Further exploration of these medications under different experimental conditions would better estimate their true clinical benefit. Certainly, the lower cost, wide accessibility, and possible clinical improvement with many of these newer unconventional remedies has encouraged their continued research. It remains to be seen which, if any, provide a more advantageous therapeutic ratio than standard agents. These observations presumably are valid, truthful, and correct; as in the case of most pharmacologic arenas, the final arbiter is the patient. Alas, these patient truths are unfortunately not as hard a science as most physicians would like.

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