 ORIGINAL ARTICLE

Natural Ingredients in Atopic Dermatitis and Other Inflammatory Skin Disease

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ABSTRACT

Active naturals in dermatology have been experiencing a renaissance. Many of the naturals that have been known for centuries to be effective for various skin conditions have now been scientifically validated with the unraveling of the pathophysiology behind their medicinal mechanism. This article seeks to present data on the clinical use of key dermatological active naturals such as oatmeal, feverfew, chamomile, aloe vera, licorice, and dexpanthenol, as well as on recent multicenter and international clinical studies that support their efficacy and safety profile for a variety of inflammatory skin conditions.

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INTRODUCTION

Atopic dermatitis (AD) is the most common inflammatory skin disease in childhood and affects about 20% of children in the industrialized world. Our current understanding of the pathophysiology has shown that the disease represents a complex interplay of genetic, immunologic, metabolic, infectious, and environmental factors. Over the past decade, research has particularly focused on the defective skin barrier due to a genetic mutation in fillagrin, an integral structural protein of the epidermis. Affected individuals are more prone to increased transepidermal water loss (TEWL) via the epidermis, increased penetration of sensitizing agents resulting in inappropriate stimulation of the immune system, and increased loss of natural moisturizing factor. In addition, the resulting T-helper 1 (Th1)/T-helper 2 (Th2) imbalance of the immune system promotes a hyperreactivity of the skin that is clinically manifest in various forms of dermatitis, and the lack of defensins as major players of their innate immunity leaves patients more susceptible to skin infections. It is increasingly evident that our treatment efforts need to focus on the correction and reversal of these pathophysiologic mechanisms. New studies to support this claim are underway and this article will present some of the latest data.

Numerous moisturizers and so-called barrier creams aim at the restoration of the compromised skin barrier function. This has been identified as key to minimizing progression of the "atopic march" and evolution into further atopic disorders such as asthma, allergic rhinitis, and eosinophilic esophagitis. The search for safe and efficacious agents has led to renewed interest in natural ingredients that have been known and trusted as "home remedies" for centuries. From among these ingredients, oatmeal, feverfew, chamomile, aloe vera, licorice, and dexpanthenol deserve particular citation because they have recently been researched more thoroughly and are considered safe and effective for various skin conditions. However, in contrast to previous experience based solely on observation and heresay, our current knowledge of these agents and their pharmacologic mechanism is based on sound scientific research and clinical studies. Based on controlled clinical data and reproducible pharmacologic compounding, these agents have been catapulted from their traditional use into modern medicine.

While topical corticosteroids remain the mainstay of anti-inflammatory treatment, and their judicious use has been shown to be both efficacious and safe, their continuous, sometimes daily, use over months raises concerns, particularly in the pediatric age group. Caregivers often shy away from the appropriate duration and intensity of required treatment due to widespread fear of side effects of topical steroids and widespread steroid phobia. Topical calcineurin inhibitors offer a second line treatment approach, but are not US Food and Drug Administration (FDA)-approved for children under 2 years of age. Their use raises concerns in parents, given the "black box" warning that remains active even after the recent FDA review of use data over the past 10 years.

The search for alternative options has rekindled the interest in natural ingredients as adjunct treatment for AD. Recent data have further corroborated that the properties of these "new naturals" reach well beyond their moisturizing effects. They are increasingly valued in modern dermatology for their additional anti-inflammatory, anti-pruritic, and skin-protectant properties.

These natural ingredients are labeled as such because they consist of extracts derived directly from plants or animal products; however, unlike some products marketed as "organic", their constituents have been dermatologically tested for the pharmacology grade purity, efficacy, and safety demanded from modern medicine.[1,2]

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Colloidal Oatmeal

Derived from the common or wild oat (*Avena sativa*), colloidal oatmeal has a long history of traditional folk use dating back to 2000 BC in Egypt and the Arabian peninsula. Oats have been used internally and externally for various conditions, most prominently skin ailments. Oatmeal baths were popular even in the 19th century for pruritic and irritant dermatoses. Colloidal oatmeal stands out among the natural products since it has even been officially recognized by the FDA for its anti-pruritic and skin-soothing properties in the context of eczema and contact allergy. It stems from dehulled oat kernels that are ground into a very fine powder that is readily dispersible in water. Most of the constituents of the powder are less than 75 microns in particle size, allowing for superior dispersion and permitting its formulation as topical skin care and bath products. Colloidal oatmeal consists of various oat fractions including 2% to 11% of lipids, up to 64% of sugars and amino acids, 12.5% to 18% of vitamins including A, E, B, and saponins, flavonoids, prostaglandin inhibitors, and just a very small fraction of 0.06% avenanthramides.

Ongoing research has provided new data on the function of each of these subfractions. Colloidal oatmeal proteins have been shown to be capable of buffering both acids and bases. Oatmeal has many components that repair or preserve barrier function. Its proteins and polysaccharides bind to the skin and provide a protective barrier to external insults. The anti-pruritic activity of colloidal oatmeal is generally attributed to its ability to maintain barrier integrity and protect against external insults, its ability to moisturize the skin and alleviate itching due to lack of hydration and abnormal subcutaneous buildup arising from abnormal desquamation, and its anti-inflammatory components, such as linoleic acid, which have been shown to reduce skin inflammation. It is able to bind to the skin and help form a barrier that reduces TEWL and also helps prevent the entry of environmental irritants. An additional barrier-protective and anti-pruritic effect derives from oatmeal's hydrocolloid effect, which creates a film that stays on the skin.[2-12]

A newly discovered oat fraction, avenanthramides are the principle polyphenolic antioxidants in oats and have been shown to exert their anti-inflammatory properties via NF-κb activation and inhibition of pro-inflammatory cytokines in keratinocytes. In one study on mice, researchers were able to demonstrate the ability of avenanthramides to block the irritation associated with contact hypersensitivity in a dose dependent response, with activity of the 3% avenanthramide formulation comparable to 1% hydrocortisone. In a skin erythema model, separated oat fractions were tested to further explore the functional properties of various oat components. Compared with other oat subfractions, the avenanthramide fraction most effectively reduced ultraviolet (UV)-induced erythema 24 hours after skin application. In preclinical models, avenanthramides were found to decrease the stimulated release of interleukin 8 (IL-8) from human epidermal keratinocytes. Significant reductions of IL-8 release were obtained with 1, 10, and 100 µg/mL avenanthramides ($P<.05$). Clinical studies indicate that avenanthramides may be of particular value in restoring the cutaneous barrier and reducing symptoms of AD. It is therefore not surprising that clinical efficacy of colloidal oatmeal has been demonstrated in such varied skin conditions as AD, contact dermatitis, fungal infections, seborrheic dermatitis, burns, and postchemotherapy dermatologic toxicity.[7-12]

New focus has been shifted onto the various lipid components within the oat subfractions. When fractionated, whole oat oil is composed of a mixture of lipids, falling into 4 main lipid classes: triglycerides, diacylglycerol, phospholipids, and free fatty acids, with smaller amounts of sterols, phosphatidylethanolamine, and other compounds. The buffering capacity of colloidal oatmeal restores the pH of damaged skin to within the normal range, a capacity that has been well documented in the medical literature since the early 1950s.

In another early clinical study, colloidal oatmeal was used as a bath and a cleanser for 3 months by 139 patients aged 21 to 91 years with various pruritic dermatoses, and was able to achieve complete or marked relief in more than 71% of these patients.[5] It has also been used successfully in the treatment of burn patients, promoting skin healing.[7] More recently, colloidal oatmeal has been shown to provide symptomatic relief of the dermatologic side effects of chemotherapy, specifically in the treatment of the acneiform eruption induced by epidermal growth factor receptor and multiple tyrosine-kinase inhibitors.[8] Similarly it has been effective in controlling the pruritus caused by erlotinib.[9]

Infants and children aged 2 months to 6 years suffering from AD, contact dermatitis, or seborrheic dermatitis were treated with a colloidal oatmeal cream and cleanser for 4 weeks. Dermatologist evaluation at weeks 2 and 4 showed significant

improvement in dryness, roughness, and itchiness using a visual analog scale, and significant improvement (P<.05) in mean scores for the Investigator's Global Assessment (IGA) and Eczema Area and Severity Index (EASI) composite scores, all resulting in a significant improvement of the Quality of Life (QOL) Index. These studies support previous clinical observations that the combination of colloidal oatmeal and emollient oils is synergistic.[4,5] In one investigation, researchers found that baths with colloidal oatmeal in an oil form soothed and cleansed the skin without irritation when used in 152 children presenting with a range of inflammatory dermatoses.

Many attribute these positive effects on skin healing to the ability of colloidal oatmeal to reduceTEWL in the skin, indicating an improvement in the skin barrier. In a clinical study of 27 female subjects using a colloidal oatmeal cream, TEWL values were significantly reduced, comparable to the efficacy of a prescription (R_x) barrier emulsion. Applying these observed properties to the skin care regimen of atopic skin showed a statistically significant (P<.01) improvement in the IGA scores and EASI composite scores, and in itch severity at weeks 2, 4, and 8 in patients ranging from 12 to 60 years of age, demonstrating the importance of proper skin care in the management of AD. These results further translated into a significant improvement of the QOL scores of enrolled patients.[12]

Most recent data are documented in an international, multicenter, open-label, 12-week study conducted in Portugal, Italy, and Greece in November 2010.[33] The objective of the study was to assess the efficacy of a soothing colloidal oatmeal emollient cream to improve the signs of atopic skin. A total of 99 patients with mild-to-moderate eczema, aged 6 months to adult, were enrolled in the study. More than 60% of enrollees were aged 5 years and under. The study protocol started with a 1-month washout period, and patients with a score greater than T0 entered the study. The patients applied the study medication to the affected eczema areas. They were instructed to continue their normal skin regimen. Evaluations were conducted at weeks 4, 8, and 12. Any patient who had a score of 0 at the 1- or 2-month evaluation did not enter the analysis. A total of 71 patients were used in the efficacy analyses. At week 12, 100% of patients had improvement in skin hydration, 96% had improvement in pruritus, 82% had improvement in scaling, and 88% had improvement in erythema. Scoring atopic dermatitis (SCORAD) scores also improved. Overall, more than 90% of patients had improvement in SCORAD at week 12. The mean percentage improvement was 37% for children aged 5 years and under, 58% for children and adolescents aged 6 to 20 years, and 48% overall.

As the result of the study it was shown that regular use of colloidal oatmeal cream has a corticosteroid-sparing effect as the inflammatory skin condition continued to improve. During the washout period, patients averaged 5.5 grams of corticoids. After 4 weeks of using colloidal oatmeal cream, the measured corticosteroid use declined by 39.4% (9.24 grams/patient). Sixty-three percent of patients felt that they used fewer corticoids/immunomodulators than prior to the start of the study.[28-32]

These are significant results when looking at the management of any chronic skin condition that has to rely heavily on repeated use of topical steroids for acute flare control and maintenance, and shows that colloidal oatmeal deserves ongoing clinical research and application in various inflammatory skin diseases.

Feverfew

Feverfew (*Tanacetum parthenium*) has, as the name implies, traditionally been used to treat fever, headache, and arthritis. More recently, experiments using human epidermal keratinocytes have shown that its antioxidant, anti-inflammatory, and anti-irritant properties are based on its inhibitory effects on various pro-inflammatory enzymes and mediators including 5-lipooxygenase and phosphodiesterase as well as tumor necrosis factor α (TNFα), IL-2, IL-4, and prostaglandin E2 (PGE2).

However, extracts from the plant that retain parthenolide are unsuitable for topical use because they often cause significant skin sensitization and irritation. This apparent limitation to its use does not apply to the parthenolide-free feverfew extract, which was specifically developed to allow the beneficial use of feverfew in topical skin care products. This extract has been refined to selectively collect the beneficial constituents from feverfew while removing the sensitizing element. The parthenolide-free feverfew extract has been proven to induce neither phototoxic nor photoallergic responses when applied to the skin in topical formulations.[2,13,14] The following examples of its clinical use are all based on the use of the parthenolide-free feverfew extract.

This formulation has particularly shown efficacy in preventing skin redness in volunteers in a dose-dependent manner. Redness was induced by the topical application of methyl nicotinate, which causes rapid vasodilatation of peripheral blood capillaries mediated by prostaglandins. Topical administrations of feverfew at different concentrations were all effective at preventing redness with increased efficacy when higher concentrations of feverfew were added.[13] In response to these encouraging results, feverfew has been evaluated for the treatment of women with sensitive skin, resulting in significant improvement in facial redness, roughness, and irritation.[14]

In another study, a moisturizer containing the extract and SPF 30 sunscreen were evaluated for the treatment of women aged 25 to 62 years with sensitive skin over 3 weeks with a similar reduction of redness, dryness, and skin irritability, as well as

increased textural skin improvement. One further practical application has been the use of feverfew in the prevention and treatment of shaving irritation.[16] Most interesting, however, are the preclinical studies using normal human epidermal keratinocytes, which showed that when feverfew extract was added immediately before UV exposure to the cells, inhibition of the release of reactive oxygen species (ROS) in a dose-dependent fashion was observed.[17,18]

A similar potent antioxidant effect was noted in an experiment measured from skin cells acquired by tape stripping. Various moisturizing products each containing different ingredients that claim antioxidantive properties were applied to the volar forearm of panelists, one of them containing feverfew extract. After 4 hours, skin cells were tape stripped and assessed for ROS ex vivo. Only the product containing feverfew significantly inhibited ROS production. Applying these results to skin in the context of UV exposure suggests potential clinical use as a sun-protective agent.

Chamomile

Chamomile has a long-standing history in folk medicine both internally and externally, mainly for gastrointestinal symptoms but also as a skin soothing agent and aromatherapy ingredient. The flower's active ingredients are flavonoids, volatile oils, courmarines, mucilages, and saccharides, which show inhibition of cyclooxygenase, lipooxygenase, and histamine. Chamomile is well tolerated when used topically, and is frequently used for minor irritations of the skin, comparable in its efficacy to 0.25% hydrocortisone cream for AD. In a study in Helsinki, 48 women who had undergone surgery for breast cancer applied chamomile cream above the wound area and almond oil below the wound area half an hour prior to radiotherapy and again at bedtime. Chamomile appeared to delay the onset of radiation dermatitis and reduced the severity grade compared with almond oil, even though neither was able to prevent radiation dermatitis altogether or prevent symptoms of itchiness and pain.[19-21]

Aloe Vera

Aloe vera has long been known for its anti-pruritic, analgesic, bactericidal, antifungal, and health-promoting effects. Active components include salicylic acid, magnesium lactate, and polysaccharides gel, which decrease thromboxane A2 and B2 and prostaglandin 2a, and function as lipid radical scavengers. Studies have in particular underscored its skin-healing properties in psoriasis.[22]

Licorice

Licorice exerts its anti-inflammatory and skin lightening properties via glabridin, licochalcone A, and liquiritin, and has been shown to be suitable even for sensitive skin. Glabridin is the main active ingredient derived from *Glycyrrhiza glabra* and is a constituent in many different botanicals. It is known to have anti-irritant effects through inhibiting superoxide anion production and as a cyclooxygenase inhibitor. The licorice extract licochalcone A is derived from a different kind of licorice plant grown in northwest China, *Glycyrrhiza inflate*. It appears to exert it's own anti-irritant effect via the same biochemical pathways. Liquiritin is a flavonoid in licorice that along with other components imparts the natural yellow color.[23,24] Studies of a skin care regimen containing a licochalcone A based cleanser, SPF 15 lotion, spot concealer, and night cream applied over 8 weeks showed good redness-neutralizing properties that were confirmed using cross-polarized photographs.[25] Liquiritin applied in the clinical setting for idiopathic epidermal dyspigmentation has been shown to exert a skin brightening effect in a vehicle controlled 4-week study.

Dexpanthenol

Dexpanthenol is another natural that has long been treasured for its skin healing and soothing properties, and historically used on superficial wounds, burns, and dermatitis. Pantothenic acid, a member of the vitamin B5 complex, is essential to normal epithelial function and a component of co-enzyme A. Studies have shown significant reduction in itching and burning in AD patients using a colloidal oatmeal bath with ceramides and dexpanthenol.[27]

CONCLUSIONS

The traditional use of natural ingredients, which was largely based on empiric evidence and folk medicine recipes, has been completely updated and scientifically validated by recent bench side and clinical research. An increasing body of scientific data now supports their use in various clinical settings, and new indications are continuously emerging. Most of the "new naturals" are specifically considered safe for sensitive skin; however, caution should be used when applying oil-based products such as tea tree oil, camphor oil, and lavender oil. These naturals have been shown to be useful as adjunct treatment in a variety of inflammatory skin conditions, including AD, contact dermatitis, drug-induced cutaneous rashes, and burn injuries. They have in particular emerged as alternative options in the treatment of pediatric patients, where the concern about potential side effects of topical steroids and/or calcineurin inhibitors remains a major consideration. These "new naturals" are expanding our treatment choices for the management of inflammatory skin disorders on an ongoing basis, with new emerging usage and research data supporting their strong reputation as safe and effective options.

DISCLOSURES

Magdalene A. Dohil MD has served as a speaker and on an advisory committee for Johnson & Johnson Consumer Companies, Inc.

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