



## Active Naturals Have a Key Role in Atopic Dermatitis

Joseph Fowler, Jr, MD, and Nanette Silverberg, MD

### FACULTY

**Joseph Fowler, Jr, MD**  
Clinical Professor of Dermatology  
University of Louisville  
Louisville, Kentucky

**Nanette Silverberg, MD**  
Director  
Pediatric and Adolescent Dermatology  
St. Luke's-Roosevelt Hospital Center  
New York, New York

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### Introduction

Atopic dermatitis accounts for 10% to 20% of visits to dermatologists.<sup>1</sup> About 90% of the cases arise before 5 years of age.<sup>1</sup> For reasons that have yet to be completely explained, the prevalence of the disease has increased dramatically over the past 50 years. In the 1950s, the prevalence of atopic dermatitis among school-aged children was 5%. Among children born after 1980, the prevalence is three- to four-fold higher. Children aged 5 to 9 years have an estimated prevalence of 17.2%. In contrast, the overall prevalence of active atopic dermatitis in the United States is 3%.<sup>2</sup>

The etiology of atopic dermatitis continues to be investigated. Regardless of the cause, however, a key feature of the disease is disruption and dysfunction of the epidermal skin barrier. The surface of the barrier, or stratum corneum, consists of corneocytes and lipids, such as cholesterol and ceramides, which fill the intercorneocyte space.<sup>3</sup> The physiologic functions of the skin barrier include maintaining hydration and repelling toxins and pathogens. Potential causes of barrier dysfunction include genetic alterations, environmental insults, contact allergens and irritants, and iatrogenic factors, such as the use of topical retinoids and corticosteroids.<sup>4-6</sup>

Barrier dysfunction in atopic dermatitis is associated with substantial loss of ceramide from the stratum corneum, alteration in the ratios of different types of ceramides, and the development of abnormal forms of ceramide.<sup>7</sup> The degree of ceramide depletion correlates with the degree of transepidermal water loss (TEWL), which is in-

creased in patients with active atopic dermatitis and accompanied by decreased capacitance.<sup>8</sup>

Studies have suggested that ceramide-dominant barrier repair emollients represent a safe and useful adjunct to the treatment of atopic dermatitis in children. For example, a ceramide-dominant, lipid-based emollient was evaluated as a substitute for standard emollients used to treat 24 pediatric patients with recalcitrant atopic dermatitis.<sup>9</sup> After 3 weeks, all but two of the patients demonstrated significant improvement on a standardized scale of atopic dermatitis disease activity. Stratum corneum integrity and hydration improved, and TEWL decreased as the barrier regained normal function.<sup>9</sup>

### Natural Ingredients and Atopic Dermatitis

Natural compounds play a major role in the management of atopic dermatitis in children and adults. Active naturals offer several advantages when caring

**Table 1 Active Naturals in the Management of Atopic Dermatitis (AD)**

- Restore physiologic barrier
- Reduce need for corticosteroid application in pediatric AD
- Possible alternative to topical calcineurin inhibitors in children <2 years of age (topical calcineurin inhibitors are indicated for children ≥2 years of age)
- Reduce and prevent cutaneous inflammation and irritation

for patients with atopic dermatitis. The compounds have the potential to help reduce inflammation and irritation, as well as promote barrier repair (Table 1). Of particular value for pediatric patients, products containing natural ingredients may help reduce the need for corticosteroids and topical calcineurin inhibitors (TCIs). They offer an alternative approach for children younger than 2 years of age, as topical corticosteroids are approved only for children 2 years of age or older.

The inherent advantages of active naturals address multiple clinical goals for patients with atopic dermatitis. Major goals of therapy include repairing and healing the barrier, restoring normal hydration and preventing excess TEWL, reducing itching and the frequency of disease flares, improving patient comfort, and improving sleep patterns and quality of life for patients and their parents or caregivers.

Several natural ingredients have proved to be especially beneficial when caring for patients with atopic dermatitis and sensitive skin. They are colloidal oatmeal,

avenanthramides (the active extracts of oats), olive oil, and shea butter.<sup>10,11</sup>

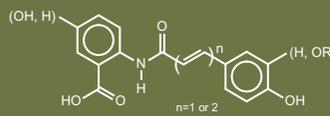
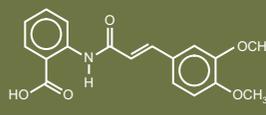
### Colloidal Oatmeal

Clinical use of colloidal suspensions—particularly oats—to treat atopic dermatitis and other inflammatory skin conditions goes back at least a half century.<sup>12,13</sup> Modern colloidal oatmeal compounds contain a mix of natural ingredients developed from extensive laboratory investigation of each component. The principal ingredients are<sup>14</sup>:

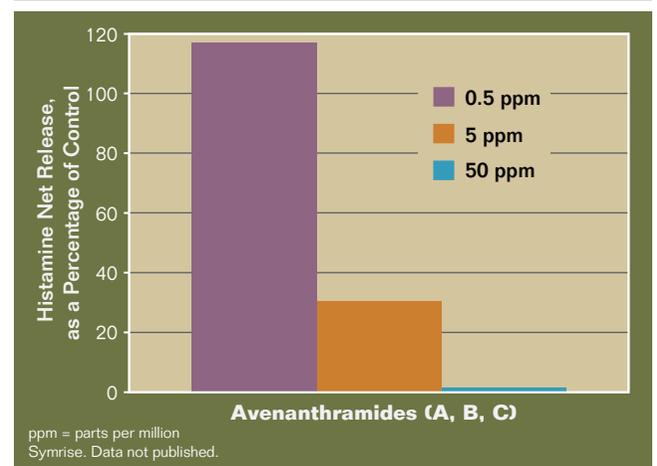
- Protein (10%-18%)—Acts as an emulsifier, promotes hydration, and promotes antioxidant activity
- Polysaccharides (60%-64%)— $\beta$ -glucan appears to have immunomodulatory activity, which could represent a modulating effect on inflammation
- Lipids (3%-9%)—Contribute to viscosity to reduce the rate of TEWL
- Antioxidant enzymes, saponins, vitamins, flavonoids, and prostaglandin synthesis inhibitors (9%-17%)—All have anti-inflammatory properties.

Colloidal oatmeal has proved to be well suited for treating inflammatory skin conditions. The natural ingredient cleanses and moisturizes, helps protect the skin barrier, and has anti-inflammatory activity. Colloidal oatmeal preparations are safe and cosmetically stable, and do not irritate the skin. Additionally, colloidal oatmeal has been shown to promote skin repair after exposure to chemicals (such as  $\alpha$ -hydroxy acids, surfactants, and bleaches) and other environmental insults.<sup>15,16</sup>

**Table 2 Antihistamine Activity**

Avenanthramides Are Analogs to Tranilast, a Topical Drug	
 <p>Cinnamoyl conjugates of anthranilic acid (Avenanthramide)</p>	<ul style="list-style-type: none"> <li>• Histamine H<sub>1</sub> receptor antagonist               <ul style="list-style-type: none"> <li>• Potent antihistamine</li> <li>• Antiallergen</li> </ul> </li> <li>• Cutaneous anaphylaxis inhibitor</li> </ul>
 <p>(Tranilast)</p> <p>Symrise. Data not published.</p>	<ul style="list-style-type: none"> <li>• Potent anti-inflammatory</li> <li>• Antioxidant lipoxygenase inhibitor</li> </ul>

**Table 3 In Vitro Antihistamine Assay**



### Avenanthramides

Avenanthramides represent only a small constituent of oats, but they can have large effects on inflammatory processes typical of atopic dermatitis (Table 2). Recent studies have traced the phytochemical activity of oats to three avenanthramides, named A, B, and C (Table 3).<sup>17</sup> Recent studies have shown that avenanthramides have multifaceted anti-inflammatory activity that includes inhibition of nuclear factor (NF)- $\kappa$ B activation in keratinocytes and reduction of both the skin immune response and the skin neurogenic inflammatory response.

One example of avenanthramides' anti-inflammatory activity came from a study that focused on the oat fractions' effects on interleukin-8 (IL-8), a potent proinflammatory cytokine that is elevated in atopic dermatitis and other inflammatory skin conditions.<sup>18</sup> Normal

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human keratinocytes were incubated with or without known IL-8 inducer tetrade-canoylphorbolacetate (TPA) in the presence of vehicle or varying concentrations of avenanthramides.

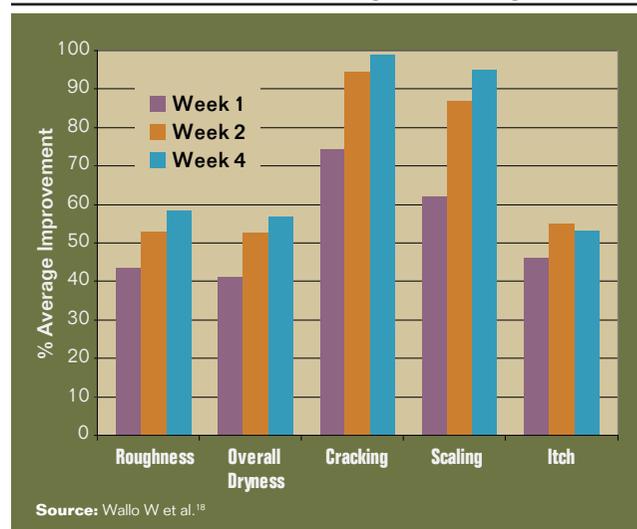
IL-8 release from TPA-stimulated keratinocytes increased dramatically compared with the unstimulated state. However, avenanthramides significantly inhibited IL-8 release from stimulated keratinocytes in a

dose-dependent manner. The investigators also demonstrated dose-dependent inhibition of NF- $\kappa$ B, a primary factor in promoting transcription of inflammatory pathways in the skin.<sup>18</sup>

Examination of the in vitro effects of avenanthramides was followed by a clinical evaluation of an oatmeal-based, avenanthramide-containing moisturizing cream in 45 patients with atopy and eczema (Table 4), characterized by moderate to severe skin dryness and itching.<sup>18</sup> The oatmeal-based cream also contained glycerin, ceramides, panthenol (a skin conditioner), and petrolatum. Patients applied the cream twice daily for 4 weeks as part of their regular skin maintenance regimen. Significant improvement in all major outcomes was documented within a week, and by the end of the study, at least 50% improvement was seen in roughness, dryness, cracking, scaling, and itching.

Another recent clinical study examined the benefits of a skin care regimen that included a moisturizing cream and a body wash containing avenanthramides.<sup>19</sup> The open-label study involved 21 patients (mean age, 32 years) who had mild or moderate atopic dermatitis involving about 5% of total body surface area. Study participants used the body wash once daily while bathing or showering and applied the cream twice daily for 2 weeks. The products were used in conjunction with the patients' existing skin maintenance regimens.

**Table 4** In Vitro Effects of an Oatmeal-Based, Avenanthramide-Containing Moisturizing Cream



Dermatologists assessed the patients at baseline and after 1 and 2 weeks. At the end of the study, all of the principal outcomes (eczema severity, itching, erythema, and scaling) had improved significantly ( $P < 0.05$ ) compared with baseline. Most patients exhibited improvement by the end of the first week.

### Olive Oil

Olive oil has been used extensively in skin care and skin diseases. The oil has numerous biologically active components, including fatty acids, tocopherols, and carotenoids. Skin-related attributes associated with olive oil include antioxidant and anti-inflammatory activity, as well as protection against ultraviolet (UV) radiation. Olive oil and compounds containing olive oil have demonstrated some efficacy for the treatment of several skin conditions, including eczematous dermatoses, rosacea, and wound healing.<sup>14,20,21</sup>

Some of the strongest supporting evidence for olive oil's favorable effects on skin has come from studies of protection against UVB exposure. For example, topical olive oil was evaluated in a model of UVB-induced skin cancer.<sup>22</sup> Three groups of mice underwent repeated UVB exposures. One group was treated topically with olive oil prior to each exposure, another group was treated after exposure, and a third group served as the control. Pre-exposure application of olive oil reduced the time to

tumor onset compared with the control group, but not the number of tumors. However, post-UVB treatment with olive oil significantly reduced the total tumor count compared with the control group and the pre-exposure group ( $P < 0.01$ ).<sup>22</sup>

Therapeutic use of olive oil in dermatologic applications has a relative paucity of supporting data. A potential for comedogenesis can be an undesirable effect of topical olive oil and may be related to the source of the ingredient. Additionally, anecdotal reports suggest a small but real risk of infection and other possibly adverse outcomes from application of contaminated olive oil to the skin.

Extracted anti-inflammatory compounds have been included in one device used to treat atopic dermatitis. As opposed to crude olive oil, the refined product appears to be safe for usage in small children.

Clinicians should ask patients or their parents or caregivers about any non-prescription substances—not just olive oil—used for therapeutic or cosmetic purposes. The advisability of using the substances also should be discussed individually with the patient.

### Shea Butter

Many cosmetic and therapeutic dermatologic products contain shea butter, but the scientific evidence to support its use remains scarce. Shea butter has moisturizing properties and contains stearic acid, which promotes and protects skin barrier health.<sup>23</sup> Derived from the fruit of the shea tree, shea butter and products containing shea butter have been used to treat varied skin conditions, ranging from blemishes and dryness to psoriasis and atopic dermatitis. Shea nut extracts have been included in one device for atopic dermatitis. However, there are no published data on the usage of shea butter or nut extract as monotherapy for atopic dermatitis. Crude extracts of shea nut may be comedogenic and/or allergenic.

### Summary

For reasons that remain unclear, the prevalence of atopic dermatitis appears to be increasing. Dysfunction of the skin bar-

rier has a central role in the evolution and progression of atopic dermatitis. Effective treatment strategies are multifaceted. Increasingly, clinicians and their patients use natural ingredients as a component treatment for atopic dermatitis. Colloidal oatmeal and the oat phytochemicals known as avenanthramides have been extensively evaluated and represent a key complement for the ongoing treatment of atopic dermatitis. Other natural substances, such as olive oil and shea butter, often are used in the treatment of atopic dermatitis, but have minimal supporting scientific evidence.

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