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CLINICAL UPDATE

The Role of Natural Ingredients in Skin Care

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The use of natural ingredients in skin care dates back to early civilizations. In the absence of modern manufacturing technology, products of nature formed the basis of skin protection and skin care. Civilizations recognized early on the dermatologic benefits of substances such as soy, oats, essential oils, and a multitude of plant derivatives.

Advances in pharmaceutical and cosmetic biochemistry and in manufacturing technology have given rise to countless chemical and synthetic products that have proven invaluable to skin care. However, modern technology has augmented, but not replaced, natural ingredients, which continue to play a central role in skin care. More than 40% of all new skin care products contain one or more natural ingredients.

The discussion that follows summarizes the ongoing contributions of natural ingredients in modern skin care. The information also illustrates the link between past and present and gives clinicians reference points to help inform patients about the role of natural ingredients in skin care and answer their questions.

Merging Science and Tradition

Until fairly recently, the long history of using natural ingredients to maintain skin health was based largely on knowledge derived from centuries of trial and error. Gradually, the skin care field has begun to develop a store of scientific evidence to support centuries-old practices. Progress in laboratory technology and science has given researchers unprecedented capability to examine the biology and chemistry of natural ingredients and provide long-missing scientific explanations for the observed effects of many natural substances.

The science continues to evolve, and the knowledge base remains thin in many instances. However, some manufacturers have made a concerted effort to provide a scientific rationale for the use of their products in dermatologic applications.

Objective evaluation of products containing natural ingredients requires a basic understanding of some key terms. "Natural" means that a substance is neither artificial nor pathologic.[1] Natural ingredients are extracted directly from plants or animal products.[2]

"Organic," often used synonymously—and incorrectly—with natural, refers to products made with agricultural ingredients that were grown without the use of pesticides. The government has further defined various levels of organic products. Only those agricultural products derived from a 100% pesticide-free environment can be labeled as 100% organic. Ingredients grown in a 95% pesticide-free environment can be called organic. Products from a 70% pesticide-free growing process can be described as "made with organic ingredients."[3]

Just because a substance is characterized as "natural" does not mean that it is free of adverse effects. Cutaneous reactions have been reported for various products containing natural ingredients. The most common reactions are allergic or irritant contact dermatitis.[4]

The following review does not represent an exhaustive list of natural ingredients used in skin care. However, it does encompass some of the most commonly used ingredients and those with the most extensive research base.

Aloe Vera

Use of aloe vera in wound healing dates back to 333 BC. The gel produced inside the plant's leaves contains salicylic acid, magnesium, and polysaccharides. In laboratory studies, the gel has demonstrated anti-inflammatory effects in the form of decreased levels and concentrations of thromboxane A_2, thromboxane B_2, and prostaglandin 2α. As a lipid-radical scavenger, aloe vera also has antioxidant properties.[5]

Clinically, aloe vera has been used to accelerate wound healing, and as an antipruritic, analgesic, anti-inflammatory, antibiotic, and antifungal.[5]

The anti-inflammatory effects of aloe vera were demonstrated in a small placebo-controlled clinical trial involving patients with psoriasis.[6] Adults with mild

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plaque-type psoriasis used topical aloe vera or placebo for 16 weeks. Healing was defined as a progressive reduction in the number of lesions and desquamation followed by reduced erythema, reduced infiltration, and a lower Psoriasis Area and Severity Index score. At the end of the study, 83.3% of patients in the aloe vera group met criteria for healing compared with 6.6% of the placebo group ($P<0.01$) (**Figure 1**).

Colloidal Oatmeal

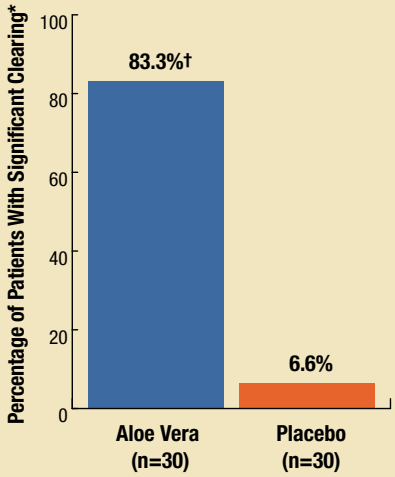
Use of oats in skin care has been documented as far back as 2000 BC. Oatmeal is one of the few natural ingredients to receive recognition from the US Food and Drug Administration (FDA). In 1989 the FDA recognized colloidal oatmeal as a safe and effective ingredient, and in 2003 the FDA approved colloidal oatmeal as a skin protectant.

Colloidal oatmeal is derived from dehulled oat kernels. Polysaccharides account for about 60% of the active components of colloidal oatmeal. Protein contributes another 10% to 15%, and lipids account for 5% to 10% of colloidal oatmeal. The remaining components include saponins, enzymes, vitamins, anti-inflammatories, and antioxidants.[4,7]

Oats contain a variety of lipids, including triglycerides, phospholipids, lecithin, and glycolipids, as well as several types of free fatty acids (oleic, linoleic, palmitic, and stearic).[8]

Of all the active components of colloidal oatmeal, avenanthramides have the most varied activity, despite accounting for less than one tenth of 1% of oat fractions. Avenanthramides have multifaceted anti-inflammatory activity. They inhibit nuclear factor κB activation, keratinocyte activation, contact hypersensitivity, and neurogenic inflammation.[7]

FIGURE 1. Aloe Vera: Skin Healing and Anti-Inflammatory Effects in Psoriasis



*Mean PASI score=2.2. †$P<0.01$.
PASI=Psoriasis Area and Severity Index.
Adapted from: Syed et al.[6]

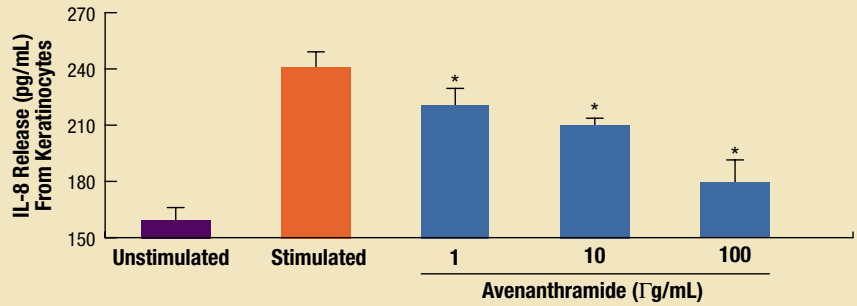
Clues to avenanthramides' anti-inflammatory effects have begun to emerge from recent laboratory studies. For example, one recent investigation focused on avenanthramides' impact on the release of the proinflammatory cytokine interleukin-8 (IL-8) in keratinocytes.[9] IL-8 levels are elevated in inflamed skin and IL-8 has potent chemotactic activity that can induce neutrophil migration to sites of inflammation. The study showed that avenanthramides reduced IL-8 release in a dose-dependent manner ($P<0.05$), whereas IL-8 release remained elevated in stimulated keratinocytes that were not treated (**Figure 2**).

Another example of the research support developed for colloidal oatmeal came in the form of a small clinical study of patients with cancer treated with an epidermal growth factor receptor (EGFR) inhibitor.[10] One common adverse effect of anti-EGFR therapy is an acneiform rash that often is severe. In this open-label clinical study, 10 patients who developed the rash were treated for a minimum of 7 days with a colloidal oatmeal lotion. All 10 patients had improvement in the severity of the rash, including six complete responses and one near-complete response (**Figure 3** on page 3). Even the three patients with partial responses had major symptomatic relief from the rash.[10]

Clinical applications of colloidal oatmeal are as varied as the components and therapeutic effects. Colloidal oatmeal formulations have been used as a skin protectant, as a skin cleanser/moisturizer, and as a treatment for poison ivy, insect bites, rashes, and dry or ashy skin.[4,7]

The skin protection properties of colloidal oatmeal were evaluated in a recent clinical study.[11] The study involved 29 women with moderate or severe dry

FIGURE 2. Reduction of Interleukin-8 (IL-8) Release by Avenanthramides



Unstimulated/Stimulated: Unstimulated or stimulated keratinocytes without avenanthramides.
Adapted from: Wallo et al.[9]

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skin on their lower legs, associated with chronic mild or moderate itching. Patients were randomized to be treated with an oatmeal-containing lotion or with vehicle, which was applied to the affected area twice daily for 2 weeks. Patients were evaluated on days 1, 7, and 14.

By clinician assessment, improvement was evident within 1 day of starting the topical agent. Virtually all of the patients had substantial improvement from baseline in dryness and scaling, 75% to 80% had a reduction in skin roughness, and 60% to 80% had substantial improvement in itching. Patient-assessed response to treatment mirrored that of the investigators.[11]

An oatmeal-based, high-potency sunscreen developed for babies was evaluated in patch tests involving adults.[12] Rated with a sun protection factor (SPF) of 45, the sunscreen maintained its protection under static conditions and in water. Tests of transepidermal water loss showed that the sunscreen significantly inhibited water loss compared with baseline and after tape stripping of the skin ($P<0.01$).

Feverfew

An extract of the *Tanacetum parthenium* plant, feverfew also has a long history of use in skin care and a good scientific basis compared with many other natural substances. Feverfew possesses antioxidant, anti-inflammatory, and anti-irritant properties. The extract has been used as an anti-inflammatory and antioxidant, for photoprotection and shaving-induced irritation, and to reduce erythema. Feverfew also can be used for sensitive skin.[4,13]

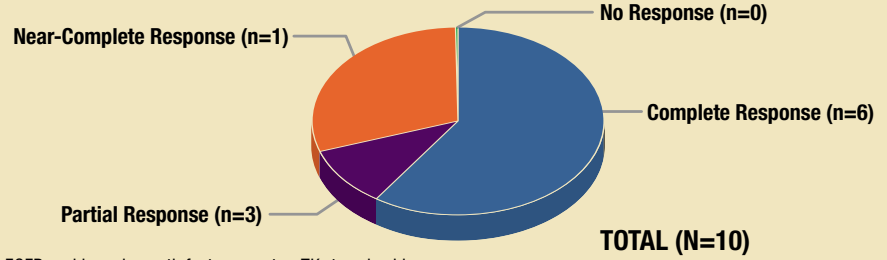
Feverfew's anti-inflammatory properties are among the most potent of natural ingredients used in skin care. In one set of laboratory tests, a dozen botanical extracts were assessed with respect to the concentration required to achieve 50% inhibition of the inflammatory cytokine tumor necrosis factor–α. By far, feverfew demonstrated the most potent inhibition, needing a concentration of 0.13 µg/mL. The next closest extract was green tea, which had an inhibitory threshold of 4.6 µg/mL (**Table**).[14]

However, unleashing the anti-inflammatory potential of feverfew required intervention by modern science to overcome a major obstacle. In its natural state, feverfew extract contains parthenolide, a strong allergen. Feverfew compounds used for clinical purposes have been purified to remove as much parthenolide as possible; hence, the term "purified feverfew extract" (PFE).

As an example of clinical research with feverfew PFE, investigators performed a placebo-controlled trial to evaluate the compound's ability to reduce ultraviolet (UV) light–induced erythema.[15] By various means of assessment, significant differences from placebo were evident within 24 hours ($P<0.05$ to $P=0.01$) and were maintained at 48 hours ($P<0.05$). The difference from placebo ranged from 18% to 28% at 24 hours and 39% to 55% at 48 hours.

Another study evaluated the benefits of feverfew PFE in patients with sensitive skin.[16] The study involved 31 women who applied a topical formulation of feverfew PFE and sunscreen in the morning and feverfew PFE moisturizer without sunscreen in the evening daily for 3 weeks. Weekly clinical evaluations revealed significant improvement in redness, roughness, and irritation, ranging from 60% to 80% compared with baseline ($P\leq0.05$). Patients noticed improvement in skin redness, blotchiness, dryness, tightness, and texture within 1 week ($P\leq0.05$).

FIGURE 3. Colloidal Oatmeal Lotion Controls Rash Associated With EGFR/TK Inhibitors



EGFR=epidermal growth factor receptor; TK=tyrosine kinase.
Adapted from: Alexandrescu et al.[10]

TABLE. Feverfew PFE Anti-Inflammatory Effects

Compound	Mediator Release TNF-α ICD50 (µg/mL)
Feverfew PFE	0.13
Green tea	4.6
Echinacea	20
Boswellia seratta	24.5
Licorice extract	54.7
Black tea	79.9
White tea	125
Bisabolol	160
Chamomile	350
Aloe vera	525
Olive leaf	675
Sage oleoresin	900

PFE=purified feverfew extract;
TNF-α ICD50 = concentration required to achieve 50% inhibition of tumor necrosis factor–α.
Data on file. Johnson & Johnson.[14]

Soy

Possessing multiple active components and potentially therapeutic activities, soy-based compounds have been evaluated in numerous dermatologic applications. Active components include phytosterols, small-protein serine protease inhibitors, Bowman-Birk inhibitor, and a trypsin inhibitor. Demonstrated effects include antioxidant/anti-inflammatory activity, enhancement of collagen synthesis, initiation of skin elastin repair, and inhibition of melanin transfer. Clinically, soy preparations have been used as anti-inflammatories, moisturizers, and cleansers and to promote photorejuvenation/photoprotection, and for skin lightening/brightening. Soy can be used in the treatment and care of sensitive skin. Soy-containing compounds have shown potential to decrease hair growth.[17-18]

Soy's depigmenting activity has attracted considerable attention. The activity derives from the effects of small-protein serine protease inhibitors, Bowman-Birk inhibitor, and a trypsin inhibitor, all of which inhibit the protease-activated receptor–2 pathway. Inhibition of the pathway reduces phagocytosis of melanosomes by keratinocytes, leading to reduced melanin transfer. The end result is reduced skin pigmentation and decreases in the diameter and pigmentation of hair.[19]

In a small clinical study involving women with melasma, a stabilized total soy extract was applied once daily to the

melasma lesions for 3 months.[20] Untreated lesions served as each patient's control. Treated lesions had a reduction in hyperpigmentation that averaged 12%, and 14 of 16 patients had improvement. The authors suggested that longer treatment might lead to even better outcomes.

The effects of a soy-based compound on skin tone and texture were examined in a 12-week placebo-controlled study involving 63 women with moderate skin roughness, blotchiness, and mottled hyperpigmentation.[21] Treatment consisted of a soy facial preparation with an SPF 30 sunscreen. Dermatologists' assessments showed significant improvement in average scores for fine lines, mottled hyperpigmentation, and skin clarity as early as 2 weeks. By 4 weeks, mean scores for all of the end points differed significantly from placebo ($P<0.05$).

Tea

Green, black, and oolong tea are all derived from the leaves of *Camellia sinensis*. Active components consist almost entirely of flavanols, including epicatechin, epicatechin-3-gallate, epigallocatechin, and epigallocatechin-3-gallate. Tea extracts have antioxidant and anti-inflammatory properties, induce apoptosis, and inhibit signal transduction, cell proliferation, and angiogenesis. Tea is used for a variety of chemopreventive and chemoprotective applications and to reverse photoaging.[22-24]

The effects of green tea extracts were evaluated in a clinical trial involving 40 women with a moderate degree of photoaging.[22] The subjects were randomized to receive 8 weeks of treatment with a combination oral-topical green tea regimen or a placebo pill and placebo cream. The active regimen consisted of a 10% green tea cream and a 300-mg green tea oral supplement, taken twice daily.

At the end of the study, clinical grading revealed no differences between the groups. Histologic grading of skin biopsies demonstrated significant improvement in the elastic tissue content of study participants randomized to the green tea regimen ($P<0.05$). However, the green tea skin treatment was associated with higher subjective scores related to irritation.[22]

UVB radiation leads to dose-dependent induction of erythema 24 hours after exposure. Investigators evaluated a topical formulation of green tea polyphenols in six healthy adults.[23] Participants were exposed to UVB minimal erythemal doses (MEDs) that ranged from 0.5 to 4.0. Comparison of treated and untreated skin areas showed that the topical green tea polyphenol compound inhibited erythema response by 100%, 97%, 86%, and 84%, respectively, at 0.5, 1.0, 2.0, and 4.0 MEDs of UVB exposure.

Summary

Traditional uses of natural ingredients have been based largely on empiric evidence. The use of natural ingredients in modern medicine increasingly is being subjected to scientific scrutiny. Accumulating evidence from basic and clinical studies suggests that natural ingredients have a role in preventing photodamage, treating inflammation, treating hyperpigmentary disorders, managing unwanted hair, and in mind-body connections (as reflected by studies of aromatherapy). At this point, the best scientific evidence relates to clinical use of oats, feverfew, soy, and green tea.

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