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Identifying Natural Ingredients and Their Use in Skin Care

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CME

EDITORIAL

ORIGINAL ARTICLES

IDENTIFYING NATURAL INGREDIENTS AND THEIR USE IN SKIN CARE

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Estimated Time to Complete This CME Activity: 1 Hour
Media/Method of Participation: Journal article, web-based post-test, and evaluation
Hardware/Software Requirements: Any web browser

Statement of Need

The dermatologic application of natural ingredients in skin care has evolved significantly in the past two decades. Research into the mechanisms and biochemistry of natural ingredients has led to the development of new technologies and formulations that provide a therapeutic benefit in the treatment of dermatologic conditions and the aging process.

Providing optimal patient outcomes continues to be a challenge in the treatment and management of dermatologic conditions. Most physicians and patients are interested in doing everything possible to optimize the treatment of their skin disease. This is especially important in treating patients with chronic disorders such as eczema, acne, psoriasis, rosacea, photodamage, and the negative effects of aging. Physicians and patients often explore the therapeutic benefits of natural ingredients as an alternative or complementary treatment to conventional methods. It is important that dermatologists remain up-to-date on the research and new advances in skin care products with natural ingredients.

Educational Objectives

This activity is a multi-specialty, evidence-based initiative designed to increase the knowledge of aesthetic practitioners by providing them with the simultaneous integration of knowledge, skills, and judgment from thought-leader testimonials, science-based research, and evidence-based data to address the difference between present patient outcomes and those considered achievable in the field of aesthetic medicine.

Upon completion of this activity, participants should be able to:

- Identify the active natural ingredients and their clinical uses in disorders of the skin.
- List key properties of natural ingredients and their relative usage in eczema, photoaging, and dermatologic conditions.
- Select potential treatment regimens for products with natural ingredients alone or in conjunction with conventional therapies.
- Recall the safety, tolerability, and efficacy of natural ingredients.

Target Audience

This activity is developed for dermatology residents and dermatologists who have an interest in the use of natural ingredients and their applications in skin care.

Accreditation Statement

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Faculty Credentials

Andrew F. Alexis MD MPH (Skin of Color Center, St. Luke's-Roosevelt Hospital Center, New York, NY), Whitney P. Bowe MD (SUNY Downstate College of Medicine, Brooklyn, NY), Magdalene A. Dohil MD (University of California, San Diego, San Diego, CA), Alan C. Logan ND (Integrative Care Centre of Toronto, Toronto, ON)

Peer Reviewer Credentials

Neal D. Bhatia MD (Laser Skin Care Center Dermatology Associates, Long Beach, CA), Zoe D. Draelos MD (Private Practice, High

Point, NC), Adam Friedman MD (Montefiore – Albert Einstein College of Medicine, Bronx, NY), Mark D. Kaufmann MD (Mount Sinai School of Medicine, New York, NY), Jeffrey M. Weinberg MD (St. Luke's-Roosevelt Hospital Center, New York, NY)

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Whitney P. Bowe MD has served on an advisory panel for Galderma Labs; as a consultant for Johnson & Johnson Consumer Companies, Inc.; and as a consultant and speaker for Tria Beauty.

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

Alan C. Logan ND has served as a consultant for Genuine Health Inc.

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Neal D. Bhatia MD has no relevant conflicts of interest to disclose.

Zoe D. Draelos MD has no relevant conflicts of interest to disclose.

Adam Friedman MD has no relevant conflicts of interest to disclose.

Mark D. Kaufmann MD has served on an advisory board for Promius Pharma and Valeant Pharmaceuticals and as a speaker for Leo Pharmaceuticals.

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Introduction

Whitney P. Bowe MD

When faced with a skin condition or with the visible signs of aging, more and more dermatology patients are seeking to benefit from products containing "natural" ingredients. These ingredients are sought as either first-line options before scheduling an appointment with a physician or utilized as adjunctive treatments alongside traditional medical interventions. Interestingly, a number of these natural/botanical compounds have been used for centuries for purported medicinal and healing properties. It has long been conjectured that these home remedies might be beneficial, but the science did not exist to support such claims. Just in the last few decades, several of these naturally derived ingredients have been subjected to rigorous scientific study. Carefully designed clinical and bench studies have begun to provide sound scientific evidence supporting the role of certain natural ingredients in skin care, turning what used to be home remedies into scientifically sound medicaments.

In this CME publication, the science behind a select group of natural ingredients will be reviewed in the context of treating cosmetic and medical conditions. Dr. Dohil will discuss the data supporting certain natural ingredients in the treatment of atopic dermatitis and a defective skin barrier. Dr. Logan and I will address the role of antioxidants in acne vulgaris and aging. Biologically active ingredients, including colloidal oatmeal, chamomile, licorice, soy, niacinamide, green tea, and feverfew, will be discussed as they relate to the skin. Finally, Dr. Alexis will focus on skin of color and the use of natural ingredients to aid in the management of hyperpigmentation. After reviewing this publication, practitioners should be in a better position to help their patients discriminate potentially effective over-the-counter products from those that lack any scientific basis for their claims.

Whitney P. Bowe MD
Clinical Assistant Professor of Dermatology
SUNY Downstate College of Medicine
Brooklyn, NY

Natural Ingredients in Atopic Dermatitis and Other Inflammatory Skin Diseases

Magdalene A. Dohil MD
Departments of Pediatrics and Medicine (Dermatology), University of California, San Diego School of Medicine, San Diego, CA

ABSTRACT

There has been a resurgence in Active Naturals in dermatology. This article focuses on recent advances in the science and pathophysiology of many naturals that have for centuries been used as home remedies. The active ingredients, clinical efficacy, and safety of various naturals, including colloidal oatmeal, feverfew, chamomile, aloe vera, licorice, and dexpanthenol, are discussed, and specific treatment indications are reviewed. Particular emphasis lies on the discussion of the clinical studies performed in children and adults that support the use of naturals in daily clinical practice.

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INTRODUCTION

Atopic dermatitis is the most common inflammatory skin disease in childhood and affects about 20% of children in the industrialized world. Our current understanding of its 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 filaggrin, an integral structural protein of the epidermis. Affected individuals are more prone to increased transepidermal water loss via the epidermis, increased penetration of sensitizing agents, which results in inappropriate stimulation of the immune system, and increased loss of natural moisturizing factor. In addition, the resulting T helper 1/T helper 2 imbalance of the immune system promotes a hyperreactivity of the skin that clinically manifests in various forms of dermatitis, and the lack of defensins as major players of our 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 in atopic dermatitis and other inflammatory skin diseases.

Numerous moisturizers and so-called barrier creams aim to restore compromised skin barrier function. This has been identified as the 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 often been known and trusted as "home remedies" for centuries. Among these ingredients, oatmeal, chamomile, feverfew, licorice, aloe vera, and dexpanthenol deserve particular citation since 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 hearsay, our current knowledge of these agents and their pharmacologic mechanism is based on sound scientific research and clinical studies. This has catapulted these agents from their traditional use into modern medicine based on controlled clinical data and reproducible pharmacologic compounding.

While topical corticosteroids are still 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 pediatric patients. Often caregivers tend to shy away from appropriate duration and intensity of required treatment because of widespread fear of side effects of topical steroids and steroid phobia. Topical calcineurin inhibitors offer a second-line treatment approach, but they are not US Food and Drug Administration (FDA) approved for children younger than two years and their use raises concerns in parents given the "black box" warning that remains active even after the recent FDA review of usage data over the past 10 years.

The search for alternative options has rekindled the interest in natural ingredients as adjunct treatment for atopic dermatitis and inflammatory skin conditions. Recent data have further proven 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, antipruritic, and skin-protectant properties. These natural ingredients are labeled as such because they consist of extracts directly derived 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]

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 because it has even been officially recognized by the FDA for its antipruritic and skin-soothing properties in the context of eczema and contact dermatitis. It stems from dehulled oat kernels that are ground into a very fine powder, which is readily dispersible in water. Most of the constituents of the powder are <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, vitamins, saponins, flavonoids, prostaglandin inhibitors, ash, and a small fraction of 0.06% of avenanthramides.[2-12]

Avenanthramides

Avenanthramides, a newly discovered oat fraction, are the principle polyphenolic antioxidants in oats and have been shown to exert their anti-inflammatory properties via nuclear factor-κB activation and inhibition of proinflammatory cytokines in keratinocytes.[6] In one particular preclinical study, 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 with hydrocortisone 1%. Clinical studies indicate that avenanthramides may be of particular value in restoring cutaneous barrier function and in reducing symptoms of atopic dermatitis. Therefore, it is not surprising that clinical efficacy of colloidal oatmeal has been demonstrated in various skin conditions such as atopic dermatitis, contact dermatitis, fungal infections, seborrheic dermatitis, burns, and postchemotherapy dermatologic toxicity.[7-12] In an early clinical study, colloidal oatmeal was used as a bath and a cleanser for three months by 139 patients aged 21 to 91 years with various pruritic dermatoses and was able to achieve complete or marked relief in >71% of these patients.[5] It has also been used successfully to promote skin healing in the treatment of burn patients.[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 two months to six years suffering from atopic dermatitis, contact dermatitis, or seborrheic dermatitis were treated with a colloidal oatmeal cream and cleanser for four weeks. Dermatologist evaluation at two and four weeks showed significant improvement ($p<.05$) in dryness, roughness, and itch using a visual analog scale, and significant improvement ($p<.05$) in mean scores for Investigators' Global Assessment (IGA) and Eczema Area and Severity Index (EASI) composite scores, resulting in a significant improvement of the Quality of Life Index (QOL).[10] 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 children (n=152) presenting with a range of inflammatory dermatoses. Many attribute these positive effects on skin healing in the ability of colloidal oatmeal to reduce transepidermal water loss (TEWL) 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 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, EASI composite scores, and in itch severity at Weeks 2, 4, and 8 in patients ranging from 12 to 60 years old, demonstrating the importance of proper skin care in the management of atopic dermatitis. These results further translated into a significant improvement in the QOL scores of enrolled patients.[12]

Feverfew (Tanacetum parthenium)

As its name implies, feverfew has been traditionally 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 proinflammatory enzymes and mediators, including 5-lipooxygenase and phosphodiesterase, as well as tumor necrosis factor α, interleukin (IL)-2, IL-4, and prostaglandin E_2. However, extracts from the plant retaining 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 purified feverfew extract, which was specifically developed to allow the beneficial use of feverfew in topical skin care products. This formulation has been proven not to induce either phototoxic or 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 purified feverfew extract. This formulation has particularly shown efficacy in the prevention of 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 administration of feverfew at different concentrations was effective at preventing redness, with increased efficacy observed at higher concentrations.[13] Encouraged by these results, feverfew has been evaluated for the treatment of women with sensitive skin, resulting in significant improvement in facial redness, roughness, and irritation.[15] In another study, a moisturizer containing the extract was compared with SPF 30 sunscreen and evaluated for the treatment of women with sensitive skin aged 25 to 62 years. Over three weeks, similar reductions in redness, dryness, and skin irritability were observed, as well

as increased textural skin improvement.[15] One further practical application has been the use of feverfew in the prevention and treatment of shaving irritation.[16] Most interesting, however, are observations in preclinical studies using normal human epidermal keratinocytes that show feverfew extract added immediately before UV exposure to the cells inhibits the release of reactive oxygen species (ROS) in a dose-dependent fashion.[17,18] A similar potent antioxidant effect was noted in an experiment measured from skin cells acquired by tape stripping. Different moisturizing products, each containing different ingredients claiming antioxidantive properties (one of them feverfew extract), were applied to the volar forearm of panelists. After four hours, skin cells were tape stripped and assessed for *ex vivo* ROS. 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 sun-protective agent.

Chamomile

Chamomile has a long-standing history in folk medicine both internally and externally, in particular for gastrointestinal symptoms, but also as a skin-soothing agent and as an aromatherapy ingredient. The flower contains as its active ingredients flavonoids, volatile oils, courmarines, mucilages, and saccharides that show inhibition of cyclooxygenase (COX), lipoxygenase, and histamine. It is well tolerated when used topically and is frequently used for minor irritations of the skin, with an efficacy comparable to 0.25% hydrocortisone cream for atopic dermatitis. In a study in Helsinki, 48 women who had undergone surgery for breast cancer applied chamomile cream above the wound area compared with almond oil below the wound half an hour before 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 itch and pain.[19-21]

Aloe vera

Aloe vera has long been known for its antipruritic, analgesic, bactericidal, antifungal, and healing-promoting effects. Active components include salicylic acid, magnesium lactate, and polysaccharides gel that decrease thromboxane A_2 and B_2 and prostaglandin 2a and function as lipid radical scavengers. In particular, studies have underscored its skin-healing properties in psoriasis.[22]

Licorice

The anti-inflammatory and skin-lightening properties of licorice are exerted via glabridin, licochalcone A, and liquiritin. Licorice 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 by inhibiting superoxide anion production and as a COX inhibitor. The licorice extract licochalcone A is derived from a different kind of licorice plant grown in northwest China, *Glycyrrhiza inflata*. It appears to exert its likewise 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 using a skin care regimen containing a licochalcone A–based cleanser, SPF 15 lotion, spot concealer, and night cream over eight 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, four-week study.[26]

Dexpenthanol

Another natural long treasured for its skin-healing and skin-soothing properties is dexpenthanol. Historically, dexpenthanol has been used on superficial wounds, burns, and dermatitis. Pantothenic acid, a member of the vitamin B_5 complex, is essential to normal epithelial function and a component of coenzyme A. Studies have shown significant reduction in itching and burning in atopic dermatitis patients using a colloidal oatmeal bath with ceramides and dexpanthenol.[27]

CONCLUSION

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 support 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. In general, naturals have been shown useful as adjunct treatment in a variety of inflammatory skin conditions, including atopic dermatitis, contact dermatitis, drug-induced cutaneous rashes, and burn injuries. In particular, they have emerged as alternative options in the treatment of pediatric patients where the concern for 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.

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ADDRESS FOR CORRESPONDENCE

Magdalene A. Dohil MD
UCSD/Rady Children's Hospital, San Diego
8010 Frost St, Suite 602
San Diego, CA 92123
Phone:.....(858) 966-6795
Fax:.....(858) 966-4040
E-mail:.....mdohil@rchsd.org

Antioxidants in Acne Vulgaris and Aging: Focus on Green Tea and Feverfew

Whitney P. Bowe MD,[a] Alan C. Logan ND[b]
[a]SUNY Downstate College of Medicine, Brooklyn, NY
[b]Integrative Care Centre of Toronto, Toronto, ON

ABSTRACT

It has become increasingly common for dermatologists in clinical practice to encounter adult acne and patient concerns related to the visible signs of aging. Oxidative stress, and lipid peroxidation in particular, is a common thread running between acne, intrinsic aging, and environmental influences on the skin aging process. The burden placed on the antioxidant defense system in acne vulgaris and skin aging is significant, and clinically relevant. Here we discuss the emerging scientific research on the extent to which oxidative stress contributes to acne and aging, and the ways in which antioxidants, green tea and feverfew specifically, may provide clinical benefit.

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INTRODUCTION

Visits to dermatology clinics for the prevention and treatment of aging skin and adult acne have increased in tandem, particularly over the last decade. In the general population, 26% of women aged 31-40 years and 12% of women aged 41-50 years have been reported to have significant, or clinical, acne vulgaris. While less is known about acne rates in adult men, mild degrees of acne remain prevalent in women, affecting approximately one quarter of women aged 41-70 years.[1] Therefore, it is not uncommon for dermatologists to simultaneously address acne and aging using various interventions. One common pathogenic thread running between acne and aging is that of oxidative stress, a destructive force that sets in motion a cascade of inflammation in the skin. In recent years, it has become increasingly clear that antioxidants, both dietary and topical, may play a beneficial role in improving clinical outcomes in acne and aging skin. Here, we discuss the role of oxidative stress in acne and aging, with special emphasis on two important antioxidant-rich botanicals—green tea and feverfew—as a means to improve acne and limit intrinsic and extrinsic aging of the skin.

The Antioxidant Defense System

Free radicals, molecules with unpaired electrons in their outer orbit, are continuously formed endogenously during the normal manufacture of cellular energy. Exposure to and production of free radicals is increased with environmental factors, including but not limited to solar radiation, cigarette smoke, and various human-made pollutants. Since free radicals are highly reactive species, capable of damaging biomolecules and cellular structures (lipids, proteins, and ultimately, DNA), humans have evolved with an efficient antioxidant defense system to minimize potential for damage. This defense system is directly supported by plant-derived antioxidant nutrients (eg, vitamins C and E) and non-nutritive phytochemicals (eg, polyphenols). The intricate antioxidant enzyme system is operated with the assistance of cofactor nutrients such as selenium and zinc. Overwhelming of the antioxidant defense system by the overproduction of free radicals has been associated with numerous chronic diseases, including those involving the skin.[2] Emerging research suggests that these antioxidants and antioxidant enzyme-supporting nutrients can influence skin health via internal and/or topical application.

Oxidative Stress in Acne

Research has shown that in both acne and aging, the normal antioxidant defense system operations can be overwhelmed. In acne, the oxidative breakdown of squalene and other skin lipids has been postulated, as long ago as 1965, to be an early contributor in the acne process. Contemporary research supports this notion.[2] Squalene, a lipid within sebum that is very sensitive to oxidation, is more than two-fold higher in acne sebum compared with healthy controls. Once oxidized, the breakdown products of squalene are highly comedogenic. Localized free radicals and the formation of peroxides, most notably hydrogen peroxide, have been shown to promote inflammation and tissue destruction in acne. Examination of comedo samples (20-30 comedones from each patient) removed from acne patients shows that lipid peroxidation is evident even in the earliest microcomedones. As the disease progresses to inflamed lesions, there is an up to four-fold increase in lipid peroxide levels.[3] Exposure of peroxidated squalene products to human keratinocyte cells stimulates production of inflammatory cytokines and upregulates lipoxygenase (LOX) activity.[4] LOX activity, and leukotriene B_4 (LTB_4) in particular, has been implicated in promoting inflammation in acne (even in the absence of *Propionibacterium acnes*), suggesting that oxidation may be an upstream factor in the acne process. Once elevated, LTB4 serves to recruit reactive oxygen species (ROS)–generating neutrophils, while its inhibition has been shown to improve acne in clinical research.[5]

The burden of oxidation in acne is significant, ultimately diminishing local antioxidants in skin and sebum. Indeed, the demand for local antioxidant support in acne is so high, it appears to re-

duce systemic levels of antioxidants in line with the clinical grade, or severity, of the condition. The blood levels of antioxidant enzymes—superoxide dismutase (SOD), glutathione peroxidase (GSH-Px)—are lower in those with long-standing acne. The differences, it should be pointed out, are not small, with GSH-Px activity reported to be 42% lower in those with acne compared with healthy controls. Interestingly, there have also been reports that the cofactor minerals involved in antioxidant enzyme operations, selenium and zinc, are lower in acne patients vs healthy controls.[2] In a recent Japanese study, acne patients were found to have lower GSH in skin samples vs age-matched healthy controls. GSH is one of the most important antioxidant chemicals in the human body, and its ability to protect cells from radical species damage is well documented. The GSH levels were not only lower in samples removed from acne-prone facial areas, they were also lower in uninvolved areas sampled from the medial side of the upper arm of acne patients.[6] This again highlights an overburdened or poorly functioning antioxidant defense system. If the antioxidant defense system is consistently taxed in acne and other disorders of excess sebum production, it might suggest that a higher risk of visible signs of aging would be apparent through adulthood. The aforementioned oxidative breakdown of squalene could certainly contribute to skin aging since squalene peroxides themselves mimic the effects of chronic ultraviolet (UV) irradiation when applied experimentally on the skin.[7] Indeed, a recent study has linked excess sebum production to decreased skin elasticity.[8]

Oxidative Stress in Aging

Aging of the skin involves intrinsic chronological aging and extrinsic pathways that are mediated by environmental factors. The chronological aging process itself, intrinsic aging, is associated with a decline in the efficiency of the skin's antioxidant defense system. Recent experimental studies show that even in the absence of environmental factors, the skin aging process involves a shift toward increased lipid and protein oxidation in association with a reduction in total antioxidant capacity.[9] Add to this the well-known influence of UV radiation and its ability to increase radical production, inflammatory cytokines (eg, interleukin [IL]-1α), and activation of nuclear factor-κB and activation protein 1. The latter two transcription factors are thought to drive the cycle of radical damage and inflammation involved in photoaging.[10] This cascade activates matrix metalloproteinase enzymes responsible for the breakdown of collagen.

The influence of UV radiation is immediate, causing an increase in oxidative stress and a diminished antioxidant capacity in the skin, one that peaks around 24 hours after exposure.[11] The burden of UV irradiation is significant, and much like the demands for antioxidant support in acne, the demand outweighs the supply, leading to depletion of antioxidants and antioxidant enzymes within the skin. The accumulation of environmentally induced free radical generation over time, in concert with declines in defense mechanisms through chronological aging, is thought to synergistically affect skin physiology.[12] Recently, investigators challenged dermatologists, in the absence of patient history or contact, to provide age assessments of anonymous healthy, nonsmoking women aged 45-60 years using only frontal and oblique facial photographs. They found that higher levels of plasma isoprostane (an objective breakdown marker of lipid peroxidation) was associated with significantly higher odds of being evaluated as older than chronological age.[13] The combination of intrinsic and extrinsic aging results in visible signs, including telangiectasias, mottled pigmentation, scaling, textural changes, fine lines, and wrinkling. Beyond the cosmetic changes, the risk of photocarginogenesis is significant.

Sunscreens are of critical importance in photoprotection and remain a front-line tool in minimizing oxidative damage through the aging process; however, the shortcomings of sunscreens have been well described, and certain portions of the UV spectrum, most notably UVA, can manage to get through these chemical or physical blocks, inevitably leading to damaging free radical production. While efficient at reducing the negative effects of UVB radiation, reports suggest that sunscreens do not adequately protect against the overall UV-induced burden, limiting free radical production in the skin by only 45%-55%.[14] Against this backdrop, there is increased attention being paid to the potential value of topical antioxidants, particularly botanical phytochemicals, as a means to enhance the efficacy of sunscreens.

Botanical Antioxidants – Background

Undoubtedly, plant-based preparations have been used for centuries as a means to encourage wound healing, treat inflammatory skin conditions, and enhance beauty. Only recently has scientific technique begun to uncover potential active ingredients, mechanisms of action, and the true extent to which clinical benefits might be observed. Plants manufacture antioxidant chemicals in their own defense against environmental assaults, and these so-called phytochemicals contribute to the taste, texture, color, and aroma of dietary plants. Most botanical phytochemicals used in contemporary dermatological preparations are classified as polyphenols, an umbrella term for more than 8,000 known plant chemicals inclusive of a phenolic chemical structure. Approximately half of the currently identified polyphenols are further subdivided into flavonoids. The flavonoids are further subdivided into numerous phytochemicals, including flavones, flavonols, flavanones, flavanonols, isoflavones, neoflavonoids, chalcones, flavanols (catechins), proanthocyanidins, and anthocyanidins.[15] Many of these phenolic structures demonstrate significant antioxidant as well as anti-inflammatory activity following consumption or topical application. Two of the more thoroughly evaluated botanical antioxidants currently in use in dermatological care are green tea and feverfew.

Green Tea and Feverfew

Tea, one of the most popular beverages worldwide, is derived from the plant *Camellia sinensis*, and the major types of tea—

green, oolong, and black—differ in the degree of fermentation of the leaves. The manufacture of green tea does not involve fermentation, and as such, contains a phytochemical profile closer to that of the growing plant. Green tea contains a variety of polyphenolic chemicals, flavonoids, as well as caffeine. Of the four major types of catechins present in green tea, the most abundant, and perhaps the most biologically active, is epigallocatechin-3-gallate (EGCG). EGCG typically accounts for 50%-80% of the total catechins in tea. However, there are numerous other potentially active flavonols in green tea, including quercetin, kaempferol, myricetin, and their glycosides. Indeed, only recently have scientists identified several dozen more polyphenolic phytochemicals within green tea via more sophisticated analytical methods.[16] There are numerous studies in humans, animals, and test-tube cell line investigations indicating that green tea phytochemicals are bioactive contributors in the prevention of cancer, heart disease, and other chronic diseases. Most often this is attributed to antioxidant and anti-inflammatory properties, yet the phytochemicals may also benefit via their influence on cell signaling and gene expression *in vivo*.

Feverfew (*Tanacetum parthenium* L.) is a daisylike perennial plant with a long history of use in traditional European, or folk medicine. Although best known for its use in headaches, feverfew has been used historically to treat various types of pain and inflammation, hence its moniker "medieval aspirin." The chemical makeup of feverfew indicates that, in addition to sesquiterpene lactones and volatile oils, there are a broad variety of flavonoids residing in the plant, including kaempferol, quercetin, apigenin, luteolin, chrysoeriol, tanetin, santin, jaceidin, and centaureidin. These phytochemicals are thought to be significant contributors to the documented antioxidant and anti-inflammatory activity of feverfew.[17]

Green Tea in Acne and Aging

There are a number of mechanisms by which green tea may be of therapeutic value in acne. Green tea is capable of preventing local and systemic declines in antioxidant enzyme activity, specifically SOD and GSH-Px. As stated above, lipid peroxidation might be one of the first steps in the acne process, and the antioxidant catechins in green tea can mitigate this process.[18,19]

Beyond its antioxidant properties, green tea demonstrates anti-inflammatory properties as well as antimicrobial activity against *P.* acnes.[20] It has also been shown to experimentally inhibit 5α-reductase activity (thereby lowering acne-promoting dihydrotestosterone) and reduce sebum production in adult volunteers when applied topically in a 3% ethanolic extract.[21,22] In addition, twice-daily application of a topical 2% green tea lotion has been shown to reduce total lesion counts by 58% after six weeks in subjects with mild-to-moderate acne.[23] This was an open-label study, and therefore, the results must be interpreted with cautious optimism. A similar study comparing a 2% tea (unspecified type of tea) lotion with a 5% zinc sulfate topical preparation demonstrated superior efficacy of the tea in reduction of acne lesions after eight weeks.[24]

There have been some 200 studies and published reports of *in vivo* and *in vitro* investigations related to the effects green tea has on the skin (search PubMed using key words "green tea" and "skin"). Green tea is frequently added to cosmeceuticals in an attempt to prevent and counter the signs of aging. All the polyphenols in green tea, and especially EGCG, confer photoprotection and act as antioxidants. Green tea polyphenols (GTPs) not only quench ROS generated by UV damage, they have also been shown to stabilize antioxidant enzymes such as GSH-Px and catalase and to inhibit lipid peroxidase and nitric oxide synthase. It has also been demonstrated that topical application of green tea extract to human skin before UVB exposure inhibited UVB-mediated erythema, reduced the number of sunburn cells, protected epidermal Langerhans cells, and reduced DNA damage. Topical application of GTPs before UVB radiation was found to inhibit UVB-induced cyclobutane pyrimidine dimer formation in a dose-dependent fashion.[25,26] In a study including 118 patients with atopic dermatitis, the consumption of three cups of oolong tea (a combination of green and red tea) for six months decreased the severity of the disease.[27] Although atopic dermatitis and acne are certainly not equivalent disease states, both are marked by chronicity and inflammation. Most of the research studies on the photoprotective and antiaging properties of green tea are in the experimental realm. However, a recent three-month, double-blind, placebo-controlled study (n=60) found that daily consumption of a green tea beverage (1,402 mg catechins per day) reduced UV-induced erythema by 25% vs baseline at 1.25 minimal erythema dose (MED).[28] Given the research showing low plasma levels of EGCG upon oral consumption,[29] the beverage study should provide optimism for further clinical benefit when green tea catechins are delivered directly (topically) to specific skin locations under environmental assault.

Feverfew in Acne and Aging

Feverfew is able to act as an antioxidant and anti-irritant by numerous mechanisms. *In vitro* studies show that feverfew can reduce the formation of lipid mediators via inhibition of the enzyme 5-lipoxygenase. It is capable of inhibiting cytokine release from activated macrophages and reducing chemotaxis of human neutrophils. The release of cytokines from activated immune cells and from keratinocytes appears to decrease in the presence of feverfew.[30-32] Furthermore, feverfew added to normal human epidermal keratinocytes immediately before UV exposure was shown to significantly inhibit the release of ROS. In this study demonstrating the antioxidant benefits of feverfew, the effects were dose dependent.[33] However, before further discussing the potential value of feverfew in clinical settings, it is important to point out that one chemical within its sesquiterpene lactone phytochemical group—parthenolide (found in the superficial leaf glands)—can lead to skin sensitization as well as irritation. Therefore, clinicians and patients should be aware that over-the-counter "natural" topical preparations containing whole feverfew or any part of its leaves in whole form is not without irritant risk. To negate the parthenolide concerns, a patented

process has been developed to purify the feverfew extract, thus removing parthenolide. Although parthenolide possesses bioactive properties that may be of relevance to pain management, the broad array of remaining phytochemicals, including the lipophilic flavonoids, retain their important anti-inflammatory and antioxidant activity[30-32] in the purified feverfew extract preparations. Vitamin C is often considered a benchmark for antioxidant activity, and it is worth noting that feverfew without parthenolide is five times more efficient at scavenging oxygen and hydroxyl radicals than is ascorbic acid. Feverfew without parthenolide has been shown to maintain skin antioxidant thiol levels in the presence of cigarette smoke, while without feverfew incubation, the dermal fibroblast thiol levels are otherwise cut in half. Moreover, pretreatment with feverfew devoid of parthenolide has been shown experimentally to reduce UV-induced IL-1α by 60% in skin samples. In a human study, two days pretreatment with a topical parthenolide-depleted 1% feverfew preparation significantly reduced erythema vs placebo at 1.0 and 1.5 MED UVB dose. Parthenolide-depleted feverfew does not work by blocking UVB, suggesting that it is an ideal candidate to enhance the antiaging benefits of sunscreens.[34,35]

Since acne is a condition where skin inflammation is visually evident, the ability of feverfew to decrease redness and irritation is clinically relevant. Adult female acne patients tend to have more mature skin that is especially prone to retinoid dermatitis or irritation following the use of benzoyl peroxide. They may have tolerated these prescriptions during their more oily teenage years, but as they age, these patients find their skin develops dry, red patches, especially around the nose and mouth. In order to help these patients tolerate their prescription regimen, soothing cosmeceuticals containing feverfew may be a useful adjunct. Purified feverfew extract has been shown to significantly prevent redness in volunteers in a dose-dependent fashion. In a study by Sur et al,[35] redness was induced by the topical application of methyl nicotinate, which causes rapid vasodilatation of peripheral blood capillaries mediated by prostaglandins. Topical administration of feverfew at concentrations of 0.5%, 0.75%, and 1.0% were all shown to prevent redness, with the effect becoming more noticeable with increasing doses.

Given its ability to reduce irritation, the clinical benefits of feverfew in aging skin are also obvious. Many of our aging patients claim that their skin is "sensitive." They desire the antiaging benefits of cosmeceutical ingredients, but they might not be able to tolerate retinol or alpha hydroxy acids. Purified feverfew extract has been studied in women claiming to have "sensitive" skin, with promising results. Thirty-one such women aged 25-62 years used a facial moisturizer containing this formulation and SPF 15 UVA/UVB sunscreen in the morning, and this formulation without SPF in the evening for three weeks. Dermatologists noted significant improvements ($P \leq .05$) in facial redness, roughness, and irritation at Weeks 1, 2, and 3. Subjects perceived significant improvements ($P \leq .05$) in skin redness, blotchiness, dryness, tightness, and texture.[34,35]

CONCLUSION

Although oxidative stress as a significant contributor to skin damage, cancer risk, and aging has been widely discussed, the critical role of the antioxidant defense system in acne is an emerging area of research. Once the antioxidant defense system is overwhelmed, a process that appears to occur rapidly in acne and with chronological aging, a cascade of events sets in motion a cycle of inflammation and further oxidative stress. Lipid peroxidation, left unchecked, only serves to contribute to the acne comedogenic and aging collagen destruction processes. Botanical ingredients such as green tea and feverfew can add an additional layer of benefit to existing front-line interventions in acne and aging; indeed, they may be a necessity in filling in the shortcomings of current sunscreens. Topical antioxidant support provides clinicians with an opportunity to address potential pathogenic pathways close to the root.

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ADDRESS FOR CORRESPONDENCE

Whitney P. Bowe MD
SUNY Downstate College of Medicine
450 Clarkson Avenue
Brooklyn, NY 11203
Phone:.....(718) 270-1229
Fax:.....(718) 270-2794
E-mail:.....wpbowe@gmail.com

Natural Ingredients in Skin of Color: Managing Hyperpigmentation

Andrew F. Alexis MD MPH
Skin of Color Center, St. Luke's Roosevelt Hospital, New York, NY
Columbia University College of Physicians & Surgeons, New York, NY

ABSTRACT

Natural ingredients have been used to improve the appearance of the skin for centuries. Over the past few decades, a growing list of naturally derived ingredients has demonstrated clinical benefits in controlled research studies. Many of these are suitable options for individuals with skin of color—a population in which disorders of hyperpigmentation are among the leading dermatologic concerns. Topical formulations containing natural skin-lightening ingredients can be considered as adjuncts or alternatives to hydroquinone in the management of melasma, postinflammatory hyperpigmentation, and other dyschromias in patients with skin of color. This article will review natural ingredients for which controlled clinical trials in the treatment of dyschromias have been conducted.

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INTRODUCTION

Multiple studies have demonstrated that dyschromias are among the most common dermatologic concerns in patients with skin of color.[1-4] Pigmentary disorders characterized by hyperpigmentation, including postinflammatory hyperpigmentation and melasma, are the most frequent dyschromias observed in this population. Hydroquinone remains the gold standard of treatment for hyperpigmentation; however, its limitations include irritation (especially at higher concentrations) and the risk of exogenous ochronosis (from long-term use). Therefore, there is increasing interest in alternatives to hydroquinone, especially natural ingredients with skin-lightening properties. Topical products containing soy, licorice extracts, niacinamide, N-acetylglucosamine, kojic acid, and lignin peroxidase have demonstrated skin-lightening effects in small controlled studies.

Soy

Small serine protease inhibitors with pigment-lightening properties have been identified in soybeans. These include soybean trypsin inhibitor (STI) and Bowman-Birk protease inhibitor (BBI), which have been shown in vitro to inhibit transfer of melanosomes to keratinocytes.[5] In addition, antioxidant isoflavones and vitamin E can be found in soybeans.[6]

Serine protease inhibitors have been shown to reduce melanosome transfer through inhibition of the protease-activated receptor 2 (PAR-2), which regulates phagocytosis of melanosomes by keratinocytes.[5,7] The PAR-2 pathway is activated by trypsin and ultraviolet B (UVB), leading to increased phagocytosis of melanosomes by keratinocytes (and hence increased transfer of pigment). Inhibition of PAR-2 activation by soy extracts (STI and BBI) leads to a reduction in melanosome transfer, which has been shown to reduce UV-induced skin pigmentation.[8]

A double-blind, placebo-controlled, 12-week study (n=63) of a moisturizer containing soy and broad-spectrum sunscreen (SPF 30) demonstrated significant improvements in mean scores for fine lines, mottled hyperpigmentation, blotchiness, skin clarity, and overall skin tone compared with placebo (containing broad-spectrum sunscreen with SPF 30) at Week 12.[6]

Niacinamide

Niacinamide is the biologically active amide of vitamin B_3. It is found in many root vegetables and yeasts. *In vitro* studies have demonstrated that niacinamide inhibits transfer of melanosomes to keratinocytes.[9] In a randomized, split-face study involving 18 Japanese women with facial hyperpigmentation (including slight to moderate solar lentigines, melasma, and freckles), a 5% niacinamide moisturizer significantly decreased hyperpigmentation compared with vehicle after four weeks.[9] The same authors also demonstrated significant skin-lightening compared with vehicle in 120 Japanese women with moderate to deep facial tans (measured by colorimeter).[9] A more recent randomized, split-face study comparing niacinamide 4% cream with 4% hydroquinone cream in the treatment of melasma (n=27) demonstrated comparable improvements by colorimetry, however, the niacinamide cream was better tolerated.[10]

N-Acetylglucosamine

N-acetylglucosamine (NAG) is a monosaccharide found in chitin, which forms the outer shell of crustaceans and insects. NAG has been shown *in vitro* to inhibit conversion of protyrosinase to tyrosinase and to modulate expression of various pigmentation-related genes.[11] NAG has demonstrated skin-lightening effects in small studies.[12]

A topical formulation containing 4% niacinamide and 2% NAG was investigated in a randomized, double-blind, vehicle-controlled trial

involving 202 white women with "moderate to moderately severe irregular hyperpigmentation" (mainly solar lentigines). At 10 weeks, the cream containing niacinamide and NAG demonstrated significantly greater improvements in hyperpigmentation than a vehicle regimen containing sunscreen with SPF 15.[12]

Licorice Extracts

Glabridin is a licorice extract derived from the root of Glycyrrhiza glabra linneva.[5] Glabridin is an inhibitor of tyrosinase that has been shown *in vivo* to reduce UVB-induced pigmentation in guinea pigs after a three-week application of a 0.5% formulation post-UVB irradiation.[13]

Liquiritin, another licorice extract with skin-lightening properties, was investigated in a double-blind, controlled, split-face study of 20 Egyptian women with melasma. In this small study using a four-point clinical severity scale with an "overall rating" from "poor" to "excellent," four weeks of twice-daily 20% liquiritin cream was superior to vehicle.[14]

Kojic Acid

Kojic acid is a chelation agent produced by fungi (eg, *Aspergillus*) and is a by-product of malted rice fermentation (used in sake manufacturing). *In vitro* studies have demonstrated that kojic acid inhibits tyrosinase via chelation of copper. Clinical studies of kojic acid as a monotherapy are lacking, but it has been studied in combination with other agents.

A 12-week, split-face, randomized study of 40 Chinese women with epidermal melasma demonstrated greater improvement with a gel containing 10% glycolic acid, 2% hydroquinone, and 2% kojic acid compared with a formulation containing 10% glycolic acid and 2% hydroquinone alone (p=0.9).[15] Another split-face study (n=39) comparing a 2% kojic acid/5% glycolic acid formulation with one containing 2% hydroquinone/5% glycolic acid showed similar efficacy between the two treatment groups.[16] However, irritation was more frequently observed in the kojic acid–containing treatment group.

More recently, a kojic acid formulation containing glycolic acid and *Emblica officinalis* extract (an agent derived from Indian gooseberry that has antioxidant and skin-lightening properties), showed comparable efficacy to hydroquinone 4% in the treatment of facial dyschromia in a 12-week, double-blind, randomized study involving 80 multiethnic subjects.[17]

Lignin Peroxidase

Lignin peroxidase (LIP) is an enzyme derived from the tree fungus *Phanerochaete chrysosporium* that degrades lignin in decaying trees causing rapid decolorization. Lignin has structural similarities to melanin, and LIP has been shown *in vitro* to degrade or depolymerize melanin.[18] A facial skin–lightening topical formulation containing LIP has recently become available.[18] In a recent randomized, split-face study (n=51) comparing the skin-lightening efficacy of LIP cream vs 2% hydroquinone cream, a significant change from baseline in melanin index was observed on day 31 with LIP cream, but not with hydroquinone 2% cream.[18] To date, no published trials of LIP in the treatment of disorders of hyperpigmentation (eg, melasma, lentigines, postinflammatory hyperpigmentation) are available.

Author's Treatment Recommendations

The current author frequently employs many of the aforementioned agents in the management of disorders of hyperpigmentation as adjuncts or alternatives to hydroquinone. A typical strategy in chronic disorders such as melasma is to use a moisturizer containing soy and sunscreens in combination with hydroquinone 4% cream during the active treatment phase (usually six months or less) and as a maintenance therapy once hydroquinone has been discontinued. When residual pigmentation is present after six months of treatment with hydroquinone, this author prefers to transition to a nonhydroquinone alternative, such as kojic acid–containing formulations in combination with a soy-containing moisturizer with sunscreen.

CONCLUSION

An increasing number of topical formulations containing natural ingredients have been investigated for their skin-lightening potential. Small, blinded, controlled studies have been conducted for formulations containing soy, niacinamide, N-acetylglucosamine, licorice extracts, kojic acid, and LIP. While there are no published studies to date that demonstrate superiority over prescription agents, cosmeceuticals containing natural ingredients can be considered as useful adjuncts to therapeutic regimens for disorders of hyperpigmentation that include hydroquinone, azelaic acid, or retinoids. Natural skin-lightening ingredients can also be considered in the long-term management of chronic disorders such as melasma, where hydroquinone-free rest periods are typically recommended to avoid the rare complication of exogenous ochronosis from long-term continuous use (especially treatment lasting greater than one year). However, there is a paucity of studies investigating the efficacy of cosmeceuticals in the treatment of specific disorders such as melasma. It is also important to note that published studies investigating the efficacy of natural skin-lightening agents in the treatment of postinflammatory hyperpigmentation are currently lacking. Notwithstanding these limitations, topical formulations containing botanical or other natural skin-lightening ingredients can serve as useful adjuncts or alternative therapies in the management of dyschromias. Further studies involving larger sample sizes and patients with specific disorders of pigmentation are warranted.

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ADDRESS FOR CORRESPONDENCE

Andrew F. Alexis MD MPH
Skin of Color Center
St. Luke's Roosevelt Hospital
Department of Dermatology
1090 Amsterdam Ave, Suite 11B
New York, NY 10025
Phone:.....(212) 523-3888
Fax:.....(212) 523-3808
E-mail:.....andrew.alexis@columbia.edu

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1. Which of the fractions in colloidal oatmeal has been shown to be particularly effective against inflammation in the skin?

   a. saponins
   b. flavonoids
   c. lipids
   d. avenanthramides
   e. ash

2. Which of the naturals has been shown to be particularly helpful in the treatment of psoriasis?

   a. colloidal oatmeal
   b. chamomile
   c. aloe vera
   d. feverfew
   e. dexapanthenol

3. Which ingredient in unprocessed feverfew is responsible for its phototoxic and contact-sensitizing properties?

   a. tanacetum enzyme
   b. parthenolide
   c. saponins
   d. lipids
   e. flavonoids

4. Which of the following clinical effects is not thought to be a benefit of feverfew extract?

   a. reduction of skin redness
   b. reduction of reactive oxygen species
   c. protection against ultraviolet exposure
   d. protection against skin irritation
   e. skin brightening

5. Free radicals are continuously formed endogenously during the normal manufacture of cellular energy. Production of free radicals is increased with exposure to environmental factors such as:

   a. water consumption
   b. solar radiation
   c. excess sleep
   d. drinking red wine

6. Which component of human sebum is both extremely sensitive to oxidation and found in two-fold higher concentrations in acne sebum as compared with healthy controls:

   a. triglycerides
   b. cholesterol
   c. squalene
   d. wax esters

7. Sunscreens limit free radical production in the skin by:

   a. 5%-15%
   b. 25%-35%
   c. 45%-55%
   d. 75%-85%

8. Soybean extracts have been shown to reduce pigmentation by which of the following mechanisms?

   a. decreased melanin production via inhibition of tyrosinase
   b. removal of epidermal melanin
   c. decreased melanosome transfer via inhibition of the PAR-2 pathway
   d. photoprotection

9. Which of the following agents reduces hyperpigmentation by degrading epidermal melanin?

   a. niacinamide
   b. N-acetylglucosamine
   c. kojic acid
   d. lignin peroxidase

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1 2 3 4 5

Enhanced my current knowledge base
1 2 3 4 5

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1 2 3 4 5

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1 2 3 4 5

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