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THE BASIC SCIENCE OF NATURAL INGREDIENTS

Release/Most Recent Review Date: August 1, 2014
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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 use of products using natural ingredients for skin care have evolved significantly in recent years. Advances in the understanding of the mechanisms and biochemistry of natural ingredients has led to the development of new technologies and product formulations that provide benefits to the management of various cutaneous disorders as well as the natural aging process. Therefore it has become increasingly important for dermatology health care practitioners of all experience levels to have access to the latest evidence-based research on advances in the understanding of product containing natural ingredients and clinical experience in their application to the practice of dermatology.

Educational Objectives

This activity is designed to increase the knowledge of dermatology clinicians and residents on the latest research and new advances in skincare products with natural ingredients. The goal of the activity is to allow participants to explore emerging research on the intrinsic and extrinsic benefits of natural ingredients and their application in patient-care. Participants will gain information on how to practically apply this research and knowledge to real, day-to-day, patient encounters.

Upon completion of this enduring material, participants should be able to:

- Identify the active natural ingredients and their clinical uses in disorders of the skin
- Classify active natural ingredients and their cosmetic benefits in skincare products
- List key properties of natural ingredients and their relative usage in inflammatory dermatoses
- Review scientific efficacy, development, and clinical studies regarding the science of natural ingredients in skin care
- Recall the safety, stability, tolerability and efficacy of natural ingredients

Target Audience

This activity is designed to increase the knowledge of dermatology clinicians and residents on the latest research and new advances in skincare products with natural ingredients.

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ORIGINAL ARTICLES
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The Basic Science of Natural Ingredients

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ABSTRACT

Herbal products have steadily gained popularity as alternatives to conventional, synthetic medications and are sought after by patients for the treatment of chronic dermatologic diseases and for cosmeceutical use. The production and distribution of botanical extracts is largely unregulated and therefore extensive research into their mechanism of action, safety, physiologic stability, and optimal dosing has been overlooked. One of the major pathways through which natural supplements, particularly polyphenols, act is via inhibition of oxidative stress and its downstream mediators. Endogenous defense mechanisms are inadequate to combat oxidative stress and therefore dietary and/or topical supplementation with polyphenols are an important complementary preventative and therapeutic strategy. This review focuses on the molecular targets of common polyphenols used in topical preparations, particularly soy, green tea, oats, curcumin, and silymarin. Continued research into bioavailability and function of these agents will help translate their therapeutic potential to treat clinical disease.

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INTRODUCTION

Herbal medicine, also referred to as botanical medicine and phytomedicine, has steadily gained popularity as an alternative to conventional, synthetic drug use.[1] In 2007, 1 out of 4 adults reported trying complementary and alternative medicine (CAM), of which nonvitamin, nonmineral, natural products were the most commonly used therapies.[2] Of note, the prevalence of CAM use was significantly higher in adults with skin disease (49.4%) as compared to the general population (36.0%).[3] In dermatologic practice, natural products are particularly sought after by patients for the treatment of chronic diseases such as acne, psoriasis and atopic dermatitis, and have become an integral component of the cosmeceutical industry.[4] The production and distribution of botanical extracts is largely unregulated and therefore extensive research into their mechanism of action, safety, physiologic stability and optimal dosing has been overlooked. However, despite the scarcity of rigorous clinical scientific data, utilization of these agents is justified by personal experience as well as their potential to target oxidative and inflammatory processes at the root of many skin diseases.[4] Elucidation of the molecular targets of these natural ingredients is essential for application in the setting of disease and prevention of adverse side effects and drug interactions.

The Impact of Oxidative Stress

Many natural agents target reactive oxygen species (ROS), which are generated as a byproduct of endogenous biologic processes and from environmental exposures, such as ultraviolet radiation, pollutants and xenobiotics.[5] ROS are defined as oxygen compounds that have a reactivity greater than that of molecular oxygen and include superoxide anion (O_2-), hydrogen peroxide (H_2O_2), hydroxyl radical (OH-) and singlet oxygen (O_2). At low concentrations, ROS exert beneficial effects by mounting a response against pathogenic organisms, inducing cellular proliferation and functioning in cell signaling pathways.[6] However, oxidative stress occurs when the production of ROS outpaces the inherent cellular antioxidant defense system.[7] This imbalance causes direct damage to DNA via oxidation of pyrimidine bases and single-stranded breaks, destruction of the cellular membrane due to lipid peroxidation, and interference with the structure and function of proteins due to modification of amino acids, particularly cysteine residues (Figure 1).[6] The accumulation of such extensive damage promotes pro-apoptotic signaling and subsequent cell death. In addition, ROS generate an inflammatory mileu by promoting the activation of transcription factors, such as nuclear factor (NF)-κB and activator protein 1 (AP-1), and the mitogen activated protein kinase (MAPK) signal transduction cascade (ERK, JNK, and p38 pathways).[7,8] NF-kB upregulates transcription of pro-inflammatory mediators, such as interleukin (IL)-1, IL-6, IL-8, and tumor necrosis factor-alpha.[9] Acting through the cell surface, these mediators generate a state of sustained inflammation by further activation of AP-1 and NF-kB. UV-induced MAPK signaling leads to increased expression of AP-1 via stimulation of cjun, a protein that combines with cfos to form the active AP-1 protein. This in turn leads to the upregulation of matrix metalloproteinases (MMP), which degrade the extracellular matrix (collagen and elastin) of the dermis and is responsible for photodamaging effects to skin.[10]

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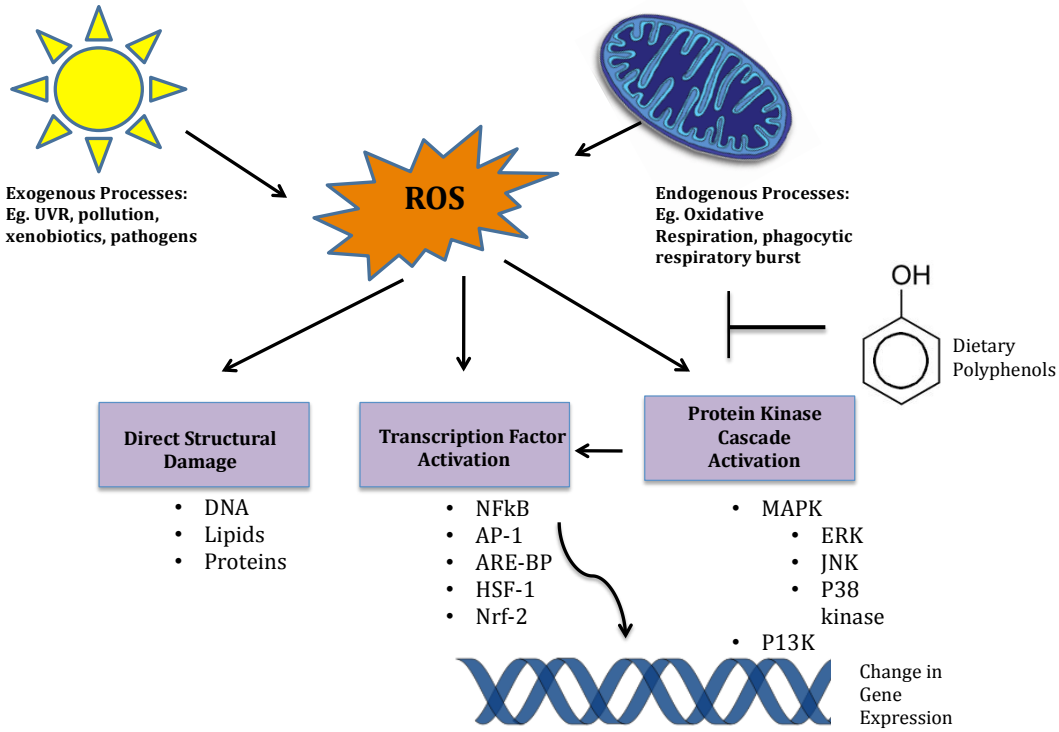
FIGURE 1. Cellular response to oxidative stress. Reactive oxygen species (ROS) originating from environmental exposures or endogenous metabolic activity exert direct cellular damage and initiate cellular signaling. ROS can activate gene transcription in two ways: a) via transcription factors, such as NF-kB, AP-1, and ARE-binding proteins (ARE-BP) that can interact directly with specific DNA motifs on promoters of target genes, or b) via activation of MAPK cascades, which in turn activate transcription factors that trigger target gene transcription. NF-kB = nuclear factor kB; AP-1 = activator protein-1; ARE-BP = antioxidant-responsive element binding proteins; HSF1 = heat shock transcription factor 1; Nrf-2 = nuclear factor (erythroid-derived 2)-like 2, MAPK= mitogen-activated protein kinase; ERK=extracellular signal-regulated kinase; JNK= c-Jun N-terminal kinase; P13K= phosphatidylinositide 3-kinase. Adapted from Scandalios et al, 2005.[11]



The type of pathway activated depends on the source and duration of the stress, as well as on the specific cell type and stage.[11]

The Innate Antioxidant Defense System

Many disease states, such as cancer, diabetes, aging and cardiovascular disease have been linked to sustained oxidative stress.[12,13] To combat these damaging effects, the body has an elaborate system of defense consisting of enzymatic (Figure 2) and non-enzymatic antioxidants. The naturally occurring enzymes include glutathione peroxidase, catalase, and superoxide dismutase (SOD), all of which neutralize ROS. SOD catalyzes the conversion of superoxide anion into hydrogen peroxide, which can then be neutralized into water and molecular oxygen by catalase and glutathione peroxidase (Figure 2). The skin has non-enzymatic antioxidant reserves, including L-ascorbic acid, glutathione, vitamin E, and ubiquinol.[14] To combat depletion, these physiologic antioxidants work in an integrated network to regenerate each other in the process. Inherent antioxidant mechanisms can be overloaded by excessive exposure to stressors and age-related decreases in enzyme production and function. Unfortunately, topical application of antioxidant enzymes has failed due to compound instability, poor cutaneous absorption and short-lived catalytic activity on the skin.[15] Looking for an alternate route, companies, and investigators have turned to nature to identify supplemental antioxidants.

Natural Supplements

Plants are an intuitive source of antioxidants as they are constantly forced to protect themselves from sun-induced oxidative damage.[14] Plants synthesize vitamin C, vitamin E, and polyphenols, naturally occurring compounds with anti-inflammatory, immunomodulatory, and anti-oxidant properties.[16] Currently 8000 polyphenols have been identified, with the most common sources being fruits, vegetables, whole grains, tea, chocolate, and wine. Polyphenols are classified chemically according to their phenolic structure, as well as the source of origin and biologic function.[17,18] Phenols exert antioxidant activity by a few mechanisms. They neutralize free radicals by donating an electron or hydrogen atom and act as direct radical scavengers of lipid peroxidation chain reactions.[19] In addition, polyphenols act as metal chelators, particularly of Fe2+, reducing the rate of the Fenton reaction and subsequent oxidation by reactive hydroxyl radicals.[20] They have been shown to induce endogenous antioxidant enzymes and inhibit xanthine oxidase.[21] Polyphenols also

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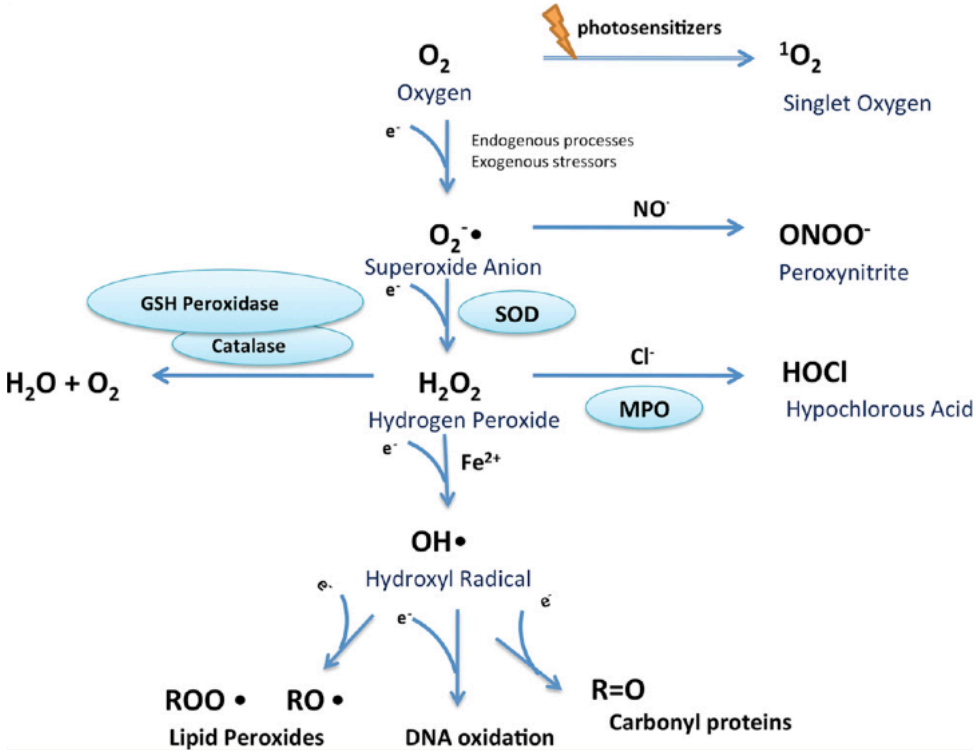
FIGURE 2. Generation of reactive oxygen species (ROS). Oxygen molecule can be converted into singlet oxygen ($^1O2$) or superoxide anion (O2-). O2- is extremely unstable and can be further converted to hydrogen peroxide (H_2O_2) either spontaneously or enzymatically by superoxide dismutase (SOD). H_2O_2 is more stable than O2- and can permeate through lipid membrane of cells. ROS can be neutralized to form water and oxygen or hypochlorous acid. H_2O_2 can also be converted to hydroxyl radical (OH-) in presence of iron ($Fe2^+$) via Fenton reaction (ie, $Fe2^+$ + H_2O_2 / $Fe3^+$ + OH- 1 hydroxyl ion). OH- can react with nucleotides, unsaturated lipids, and amino acids or be neutralized to water. GSH, Glutathione; O^2, molecular oxygen. Reprinted from *Journal of the American Academy of Dermatology*, Vol 67, Chen et al. The role of antioxidants in photoprotection: A critical review, 1013-1024, (2012), with permission from Elsevier



have many potential targets in the inflammatory cascade, such as Bax, Bcl-2, caspases, c-Fos, IκB kinase, PI3-kinase, and NF-κB to name a few.[22] The antioxidant capacity of phenolics varies depending on the chemical ring structure, particularly the number and arrangement of hydroxyl group and ring substituents, and the ionization state and stability of resulting phenoxy radicals.[23]

One common method of classification is to divide polyphenols into flavinoid and nonflavinoid phenolics (Figure 3). All flavinoids consist of two benzene rings linked by a heterocyclic pyrone C ring in contrast to non-flavinoids, which include a heterogenous range of compounds. Flavinoids are the most common polyphenol found in the human diet, with over 4000 identified, and have thus attracted the most attention.[17,24] To provide a better understanding of the mechanism of action of natural ingredients, the available data on several commonly used polyphenols will be reviewed and their applications for dermatologic disease, particularly protection from UV damage, will be explored.

Soy

Soy beans are a rich source of isoflavones and contain high concentrations of genistein, daidzein and glycitein. Isoflavones are a type of phytoestrogen, which due to the structural similarity to estradiol can bind to both ER-ß and ER-α receptors.[25] As an estrogen analog, soy isoflavones have been utilized to treat post-menopausal symptoms, including hot flashes, bone loss and skin ageing. It has been hypothesized that genistein reduces skin damage particularly through estrogen receptor binding, and has been considered as an alternative to hormone replacement therapy (HRT) as a means of avoiding the adverse effects of HRT. In addition to its estrogenic activity, the role of isoflavones in skin ageing is likely due to its antioxidant properties. Genistein is a potent antioxidant and has been shown to reduce 8-hydroxy-2'-deoxyguanosine (8-OHdG) formation (a product of DNA oxidation), scavenge hydrogen peroxide and superoxide anion[26] and induce increased activity of antioxidant enxymes, such as SOD, catalase and glutathione reductase.[27] In an in vivo study, pretreatment with genistein resulted in inhibition of cjun, the heterodimer of AP-1, which stimulates the breakdown of collagen via enhanced MMP expression. This resulted from genistein's antioxidant activity, particularly its inhibition of the ERK and JNK MAP kinases that activate AP-1.[10] Soybeans have also been shown to reduce the clinical signs of aging by inducing elastin promoter activity

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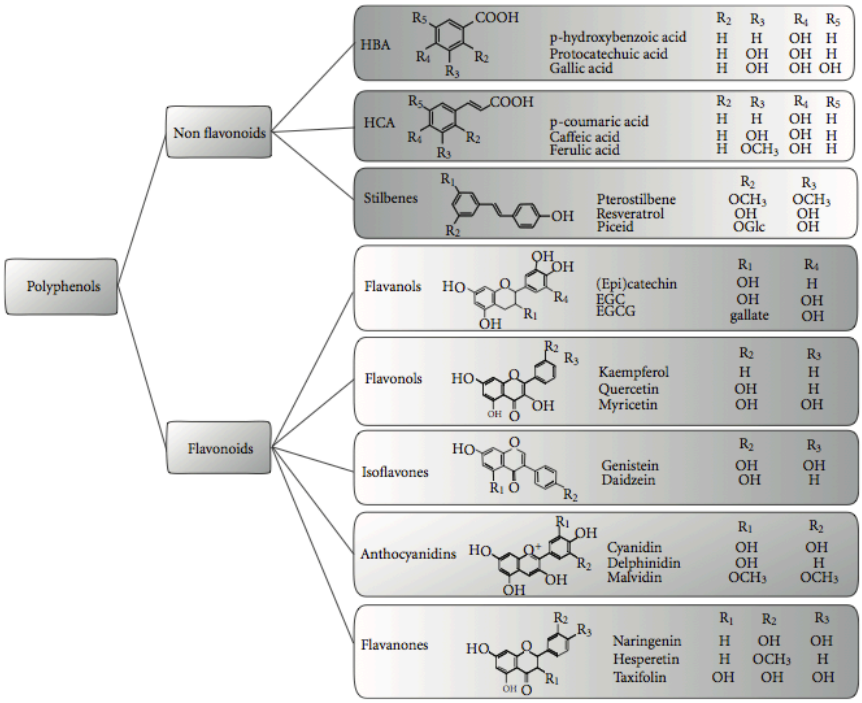
FIGURE 2. Structures of polyphenols. Polyphenols are a group of naturally occurring phytochemicals, which are present in high amounts in fruits, vegetables, and natural products and are characterised by the presence of multiple hydroxyl groups on aromatic rings. These compounds are divided into two main categories, the flavonoids and non-flavonoids, based on the number of phenol rings and the way in which these rings interact. For the flavonoid group, the major differences between the individual groups arise from the hydroxylation pattern of the ring-structure, the degree of saturation of the C-ring, and the substitution of the 3-position. HBAs, hydroxybennzoic acids; HCAs, hydroxycinammic acids. Reprinted from David Vauzour, "Dietary Polyphenols as Modulators of Brain Functions: Biological Actions and Molecular Mechanisms Underpinning Their Beneficial Effects," Oxidative Medicine and Cellular Longevity, vol 2012, Article ID 914273, 16 pages, 2012. doi:10.1155/2012/914273.



and inhibiting elastase degradation of fibers.[28] Isoflavones also reduce UVB-induced MMP-1 expression, thus inhibiting collagen degradation, but have not been shown to influence collagen synthesis de novo.[29]

Soy protein has perhaps garnered the most attention for its ability to lower cholesterol levels and its antiatherogenic effects attributed to its antiproliferative and antioxidative activity.[30,31] Genistein reduces lipid peroxidation, prevents antioxidant enzyme depletion and decreases hydrogen peroxide formation.[32] Irradiation of soybeans has been shown to increase the genistein and daidzein content, which was correlated with increased hydroxy radical scavenging activity.[33] Genistein protects against hydrogen peroxide induced DNA damage[34] and also inhibits UVB-induced apoptotic changes, including caspase 3 and P21.[35]

Green tea

Green tea is prepared from the plant *Camellia sinensis* and sold as fresh or dried unfermented leaves. It contains high quantities of monomeric catechins, the major ones being epicatechin (EC), epigallocatechin (EGC), epicatechin gallate (ECG), and epigallocatechin gallate (EGCG).[36] Catechins are considered responsible for the physiologic effects of green tea observed in vitro, with EGCG recognized as the most abundant and biologically active polyphenol at the cellular level.[37,38] It is believed that tea polyphenols exert their effects by binding to and activating specific cellular membrane receptors. However, recent evidence has revealed that catechins can be incorporated into the plasma membrane, where they can translocate into the cytoplasm in a manner akin to endocytosis and interact with different intracellular molecular targets.[39] Catechins exhibit broad antioxidant activity via direct scavenging of free radicals, reduction of inflammatory cytokines and downregulation of ROS producing enzymes. In addition, tea polyphenols have been shown to upregulate SOD, catalase and glutathione peroxidase and act as metal chelators.[40] However, there is evidence for significant pro-oxidant activity as EGCG has been shown to induce apoptosis, primarily in cancer cells, via the generation of hydrogen peroxide and superoxide. This dichotomous spectrum of pro and anti-oxidant properties is likely cell specific, but some have suggested that the generation of low concentrations of ROS's in normal cells may induce cellular resistance to higher levels of oxidative stress.[37] Green tea is a UV damage protecting agent inhibiting carcinogenic markers and UV-induced oxidative stress, including suppression of AP-1, NF- κB, STAT-1 and the MAPK cascade.[4,41] In addition, it protects against PUVA induced

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damage and has been shown to induce apoptosis in UV damaged cells by shifting the bax/bcl-2 ratio in favor of apoptosis. Both topical application and oral consumption protects against UV induced carcinogenesis, and decreases carcinogenic markers in tumors including CD31, VEGF, MMP-2, and MMP-9.[42]

Oats

Oats (*Avena sativa*) consist of a large range of phytochemicals including carbohydrates, proteins, lipids, flavonoids, avenanthramides, tocols, alkaloids, saponins, and sterols.[43] Due to the large lipid content, oat grains contain a variety of compounds with antioxidant activity to prevent lipid peroxidation.[44] These primarily include glyceryl esters of caffeic and ferulic acids, avenanthramides and alpha-tocopherol.[45] Unique to oat grain are avenanthramides, alkaloids that consist of anthranilic and hydroanthranilic acid linked through an amide bond to one of several hydroxycinnamic acids. Though only 0.06% of total oat content, this bioactive element is a major source of the observed anti-oxidant and anti-inflammatory properties of oats. There are twenty-five structural varieties of avenanthramides, but the three predominant types are formed from hydroxyanthranilic acid and *p*-coumaric, ferulic, or caffeic acids.[43,46]

Oats have well-characterized cardioprotective effects, including inhibition of atherosclerosis and hypertension and have displayed anti-inflammatory, anti-pruritic, and antioxidant activity when applied topically to the skin.[46,47] The avenanthramides possess elevated antioxidant activity compared to other oat phenolic compounds, and seem to be the source of oat's antioxidant activity.[48] Avenanthramides primarily act via inhibition of NF-kB signaling by inhibition of IkB- degradation, which subsequently decreases the production of pro-inflammatory cytokines, such as IL-8.[49] Dihydroavenanthramide D, a synthetic analog of avenanthramides, was shown to inhibit UVB-induced ROS generation, phosphorylation of MAPKs, activation of NF-kB and AP-1, and MMP-1 and MMP-3 expression.[50] Oat bran extracts decreased H_2O_2-induced human dermal fibroblast injury through the enhanced activity of SOD and a decrease in the malondialdehyde (MDA) level.[51] *A. sativa* exerts anti-inflammatory activity by inhibiting phospholipase A2 in keratinocytes, thereby decreasing the release of the arachidonic acid from phospholipids and subsequent eicosanoid formation.[52,53] Topical application of avenanthramides has also been found to reduce neurogenic inflammation and edema associated with contact hypersensitivity.[49] The flavinoids in oats are another source of anti-inflammatory activity, providing protection against UVA radiation owing to their ability to absorb light in the 320-370nm range.[44] Another component of oats, tocopherols (vitamin E), has dual functionality as anti-inflammatory and anti-photodamage agents and protects the skin from free radical damage.[54] These agents combined provide oats with its unique therapeutic potential.

Curcumin

Curcumin, *o*-methoxyphenol derivative, is the bioactive component of the spice, turmeric (C. longa), used for centuries in the Ayurvedic tradition for its medicinal properties. Polyphenolic curcuminoids constitute approximately 3% to 5% of most turmeric preparations, and is the source of turmeric's deep yellow color.[55] Turmeric contains three major curcuminoids: curcumin (also referred to as curcumin I or diferuloylmethane), desmethoxycurcumin (curcumin II), and bisdesmethoxycurcumin (curcumin III). There has been renewed interest in clinical translation of curcumin due to its antioxidant, anti-inflammatory, wound healing and antibacterial properties. Curcumin exerts anti-inflammatory activity by inhibiting multiple levels of the NF-κB, AP-1, and JNK signaling pathways, leading to decreased expression of pro-inflammatory cytokines such as TNF-α, interleukins (IL-1, IL-2, IL-6, IL-8, IL-12) and chemokines. In addition, curcumin has been shown to decrease inducible nitric oxide synthase (iNOS) activity and the activation of p38 MAPK.[56,57] Curcumin acts on the arachidonic acid pathway by inhibiting cyclooxygenase (COX)-2 expression and the downstream synthesis of prostaglandin (PG)E_2, and inducing apoptosis in cells that constitutively express COX-2.[58] One of the proposed mechanisms for COX-2 inhibition is interference with the IκK signalling complex responsible for phosphorylation of IκB and the subsequent activation of NF-κB.[59] Curcumin also acts as a potent antioxidant by inhibiting ROS generation, scavenging O2– and OH radicals, and increasing endothelial heme oxygenase-1 (HO-1) protein expression and enzymatic activity.[60,61] This protein, induced by cellular stress, degrades heme to the anti-oxidant biliberdin and carbon monoxide (CO) and is important in defending the body against oxidant-induced injury. However, clinical application of curcumin has been limited by to its low bioavailability, rapid biodegradation, and bright yellow color when applied topically.

Silymarin

Silymarin is an extract of the milk thistle plant (*Silybum marianum*) concentrated in the fruit and seeds, and is composed of three flavinoids: silybin, silydianin, and silychristine. Silybin is the most biologically active and constitutes 70-80% of the flavinoid content. Silymarin is most known for its role in treating hepatic disorders including alcoholic liver disease, cirrhosis and hepatitis,[62] effects due in part to its anti-inflammatory and antioxidant properties.[63] Silymarin has been shown to decrease lipid peroxidation as a result of ROS scavenging and its ability to increase the cellular content of glutathione (GSH).[64] Both in vitro incubation and in vivo treatment with silymarin resulted in increased SOD expression,[65] and it has displayed scavenging activity against hydroxyl radicals, though not against hydrogen peroxide or superoxide anion radical.[66] Silymarin proved efficacious in several models of oxidative stress to the liver, kidneys, and pancreas, especially in reducing the toxic effects of free radical generating drugs.[63] Silymarin selectively inhibits the 5-lipoxygenase pathway, particularly leukotriene B4 (LTB4) formation, with no effect on prostaglandin synthesis.[67] Silymarin

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suppresses the lipopolysaccaride (LPS)-induced production of nitric oxide in macrophages and was shown to decrease iNOS mRNA and its protein expression by inhibiting NF-κ B/Rel activation.[68] In the inactive state, NF-ê B remains complexed to the inhibitory protein I- κB. However, upon activation by various signals, NF-κB can translocate to the nucleus and bind to the kappa B motif of the target gene.[63] Silymarin has been shown to inhibit many steps in the NF-κB pathway; it blocks TNF alpha and UV-induced activation of NF-κB, translocation to the nucleus and κ B DNA binding and gene expression. Interestingly, the effects of silymarin on NF-κB activation are specific, and do not impact AP-1 activation. Silymarin can also inhibit the TNF-induced activation of MAP kinase kinase and c-jun kinase and mitigated TNF-induced cytotoxicity and caspase activation.[69,70]

Topical administration

Polyphenols can be obtained through both diet and oral supplementation but these methods are limited by poor systemic bioavailability and variability of gut metabolism.[16] Supplementing skin with a topical antioxidant is a more intuitive way of directly replenishing the skin's endogenous antioxidants that are depleted from constant UV exposure.[71] Various studies have shown that there is a greater amount of antioxidants in the epidermis compared to the dermis as the epidermis is in direct contact with oxidative stressors. However, due to irradiation damage, antioxidant activity in the upper layers of the stratum corneum decreases over time.[72] Topical polyphenol formulations have been shown to have good permeability in the stratum corneum, with higher concentrations in the outermost layer, thereby targeting the site of antioxidant loss.[72] In one study evaluating the penetration of polyphenols into the stratum corneum and underlying tissue, 90% of phenolic content was retained in the stratum corneum, with only 10% in underlying tissue. Catechins had greater permeability compared to curcumin and resveratrol, but this observed effect was greatly impacted by solubility in the delivery vehicle chosen.[71] Passive delivery of polyphenol extracts is greatly dependent on the formulation, which affects the permeability of the active agent into deeper skin layers. The most common delivery agents currently employed are gels or emulsions, which have shown efficacy for topical polyphenol delivery.[15] As antioxidants are inherently unstable, creation of a stable formulation has been a challenge.[14] Proper investigation into the optimal concentration and formulation is required for standardization and maximization of polyphenol delivery to skin.

CONCLUSION

Endogenous defense mechanisms are inadequate to combat oxidative stress and therefore dietary and/or topical supplementation with polyphenols are an important complementary preventative and therapeutic strategy. These natural agents have broad anti-inflammatory and anti-oxidative properties, targeting many different cellular responses to ROS stimulation. Though most of the evidence for the protective effects of polyphenols are derived from in vitro and animal studies, epidemiologic studies do suggest an improvement with polyphenolic supplementation on cardiovascular markers in particular. Continued research into bioavailability and function of these agents will help translate their therapeutic potential to treat clinical disease.

DISCLOSURES

Adam Friedman has been an investigator, consultant, or speaker for Johnson & Johnson, Amgen, Valeant, Onset, Loreal, and Salvona. Holly Gunn and Aimee Krausz have not disclosed any relevant conflicts.

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1. Which transcription factor do free radicals up-regulate that ultimately leads to collagen degradation?

a. NFkBu

b. HSP-1

c. AP-1

d. IL-1

2. Which polyphenol in oats has a strong antioxidant and anti-inflammatory potential and works in polar and nonpolar environments?

a. Avenanthramides

b. Benzoic acids

c. Cinnamic acids

d. Flavanols

3. Which intrinsic antioxidant do soy isoflavones increase in quantity and activity?

a. Glutathione peroxidase

b. Catalase

c. Glucose-6-phosphatedehydrogenase

d. Superoxide dismutas

4. Which natural plant has been studied and shown to have antioxidant, anticarcinogenic, antimicrobial, and anti-inflammatory properties?

a. Mushrooms

b. Soybeans

c. Oats

d. Tumeric

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