

Investigating Cosmeceutical Efficacy: Flavonoids

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How many times have dermatologists been asked if cosmeceuticals really work? How many times have dermatologists wished an answer was available? Unfortunately, it is not easy to compose a succinct answer to this question. I think a correct answer might be that cosmeceuticals work depending on the ingredients and user expectations. If the consumer is looking for increased tactile softness, cosmeceuticals are fabulous; however, if the consumer is looking for a reversal of facial folds, cosmeceuticals are ineffective.

Cosmeceuticals may represent an ever-expanding field in dermatology with unrealized promise. Cosmeceuticals extend beyond cosmetics to enhance skin functioning and return the skin to a more youthful state. For example, wrinkle-reducing moisturizers, antioxidant serums, and skin lightening salves all fall into this category. Cosmeceuticals are somewhat confusing because both prescription and over-the-counter products have been labeled with this term. Prescription cosmeceuticals include topical retinoids for improving dermal collagen production, topical minoxidil for enhanced scalp hair growth, and eflornithine for facial hair growth reduction. Cosmeceuticals also include over-the-counter products, such as sunscreens and antiperspirants. This article discusses only cosmeceuticals for appearance improvement.

A discussion of the efficacy of all cosmeceutical ingredients would be impossible, thus I have chosen to focus on the category of flavonoids and the published evidence available to demonstrate their efficacy. Flavonoids are aromatic compounds that typically have a yellow color and are found in plants. Five thousand flavonoids have been identified with a chemical structure possessing 15 carbon atoms and a variety of biologic activities (Table).¹ Flavonoids can be divided into flavones, flavonols, isoflavones, and flavanones. Each has a slightly different chemical structure.

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Currently, the most common isoflavones are derived from soy, curcumin, silymarin, Pycnogenol, and *Ginkgo biloba*. Each of these sources will be discussed with studies from literature to support their efficacy.

Soy

Fermented soy contains 2 primary isoflavones: genistein and daidzein. These isoflavones function as phytoestrogens when orally consumed and have been credited with the decrease in cardiovascular disease and breast cancer seen in Asian women.^{2,3} Other purported systemic benefits include improvement in immunity,⁴ reduction of prostate cancer,⁵ and improvement in cognition.⁶ Some of the cutaneous effects of soy have been linked to its estrogenic effect in postmenopausal women. Topical estrogens have been shown to increase skin thickness and promote collagen synthesis.⁷ Genestein has also been reported to function as a potent antioxidant scavenging peroxy radicals and protecting against lipid peroxidation in vivo.⁸ These are the results from human studies that have been published to date.

Other interesting soy research was performed on rodents. A study on mice documented the ability of soy to protect against UVB-induced skin damage where a topical application of nondenatured soy extracts reduced UVB-induced cyclooxygenase-2 expression, prostaglandin E2 secretion, and inhibited p38 MAP kinase activation.⁹ It is unknown whether this data from rodents translates into UVB photoprotection in humans.

Genestein and daidzein are found in postmenopausal antiaging oral supplements. It is interesting that many gynecologists are hesitant to allow patients with breast cancer to take oral soy supplements to prevent hot flashes if they have estrogen receptor-positive breast cancer. While there are no studies to confirm that oral fermented soy increases the risk for breast cancer, there are enough concerns to wonder if phytoestrogens are biologically active in the human. This is where data ends and the supposition begins.

Curcumin

Curcumin is a well-known ingredient recently discovered to have potent antioxidant qualities. It is the primary

Flavonoid Mechanisms of Action

- Photoprotection against UVB
- Quenching of reactive oxygen species
- Metal chelation
- Inhibition of targeted enzymes
- Hormonal modulation
- Anti-inflammatory activity
- Microorganism growth inhibition
- Antioxidant effect of multiple organ systems

ingredient in a skin care line designed for atopic dermatitis. Curcumin is used as yellow food coloring in everything from prepackaged snack foods to meat. It is sometimes used to provide a natural yellow color in skin care products that claim to be free of artificial ingredients. Curcumin comes from the rhizome of the tumeric plant and is consumed orally as an Asian spice frequently found in rice dishes to color white rice yellow. The color yellow is often undesirable in cosmetic preparations because it is typically associated with oxidative spoilage.

Tetrahydrocurcumin, a hydrogenated form of curcumin, is off-white in color and can be added to skin care products not only to function as a skin antioxidant, but also to prevent the lipids in the moisturizer from becoming rancid. Cosmetic chemists say the antioxidant effect of tetrahydrocurcumin is greater than vitamin E. Published reviews purport that the antioxidant benefits arise when curcumin quenches oxygen radicals and inhibits nuclear factor- κ B.¹⁰ The effects of curcumin as a topical antioxidant in the skin have not been as well studied as its oral ingestion in rodents for the correction of cystic fibrosis defects and inhibition of tumor proliferation.¹¹

The only problem with topical application of tetrahydrocurcumin is the pungent smell of the product and the stinging induced when applied to open wounds. For this reason, curcumin is used more in therapeutic, rather than cosmetic, product formulations.

Silymarin

Another family of flavonoids comes from the milk thistle plant *Silybum marianum*, which belongs to the aster family of plants including daisies, thistle, and artichokes. The plant is named milk thistle because it produces a white,

milky sap, and the oldest recorded use of the extract was to enhance human lactation. The cosmeceutical extract is termed silymarin and contains 3 flavonoids derived from the fruit, seeds, and leaves of the plant. These flavonoids are silybin, silydianin, and silychristin.

Homeopathically, silymarin is used to treat liver disease; however, it is also a strong antioxidant that prevents lipid peroxidation by scavenging free radical species. Its antioxidant effects have been demonstrated topically in hairless mice by the 92% reduction of skin tumors following UVB exposure.¹² The mechanism for this decrease in tumor production is unknown, but topical silymarin has been shown to decrease the formation of pyrimidine dimers in a mouse model.¹³ It has also been found to improve the healing of burns in albino rats.¹⁴

Silymarin is found in a number of high-end moisturizers for benign photoaging to prevent cutaneous oxidative damage and reduce facial redness. A double-blind, placebo-controlled study in 46 subjects with stage I to III rosacea found improvement in skin redness, itching, hydration, and papules.¹⁵ This was felt to be due to silymarin's direct activity on modulating cytokines and angiokines. Other well-controlled human trials are lacking.

Pycnogenol

Pycnogenol is an extract of the French marine pine bark *Pinus pinaster*, which grows only on the southwest coast of France in Les Landes de Gascogne. The extract is a water-soluble liquid containing several phenolic constituents, including taxifolin, catechin, and procyanidins. It also contains several phenolic acids, including *p*-hydroxybenzoic, protocatechuic, gallic, vanillic, *p*-coumaric, caffeic, and ferulic.¹⁶ It is a trademarked ingredient that is sold for oral consumption as a preventative for cardiovascular disease,¹⁷ a treatment for diabetic microangiopathy,¹⁸ and a pain reliever for muscle cramps.¹⁹ It is an effective free radical scavenger that can reduce the vitamin C radical, returning the vitamin to its active form.²⁰ In turn, the active vitamin C regenerates vitamin E to its active form, leaving the natural oxygen scavenging mechanisms of the skin intact.²¹

Pycnogenol is consumed orally to enhance the production of nitric oxide, which inhibits platelet aggregation in coronary artery disease. In B16 melanoma cells, it was shown to inhibit tyrosinase activity and melanin biosynthesis.²² Many discussions of antioxidant flavonoids include a mention of Pycnogenol, but quality data are limited.²³

Ginkgo Biloba

Ginkgo biloba, also named the maidenhair tree, is the last member of the Ginkgoaceae family, which dates back

approximately 200 to 250 million years ago. For this reason, ginkgo contains flavonoids not found in other botanicals. It possesses bilobalide (a sesquiterpene), ginkgolides (diterpenes with 20 carbon atoms), and other aromatic substances such as ginkgol, bilobdol, and ginkgolic acid. It is a plant with numerous purported benefits that has been a common part of homeopathic medicine for 4000 years.

The ginkgo's leaves are said to contain unique polyphenols such as terpenoids (ginkgolides, bilobalides), flavonoids, and flavonol glycosides that have anti-inflammatory effects. These anti-inflammatory effects have been linked to antiradical and antilipoperoxidant effects in experimental fibroblast models.²⁴ Ginkgo flavonoid fractions containing quercetin, kaempferol, sciadopitysin, ginkgetin, and isoginkgetin have been shown to induce human skin fibroblast proliferation in vitro. Increased collagen and extracellular fibronectin were also demonstrated by radioisotope assay.²⁵ Thus, ginkgo extracts are added to many cosmeceuticals to function as antioxidants and promoters of collagen synthesis based on nonhuman models of oxidative damage.

Summary

This article was written based on a December 2008 Medline and Google Scholar search. It was truly amazing to realize how few scientific studies had been conducted on the flavonoids discussed herein. With the widespread use of these ingredients, many more studies should have been conducted. Perhaps this is why it is so difficult to tell patients which cosmeceuticals actually work. For the most part, medical science does not know.

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