Efficacy and safety of innovative cosmeceuticals

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Abstract
The research and development of cosmeceuticals is booming in recent years. Many substances, either from botanical, animal, or chemically synthesized sources, are tested or investigated as the active ingredients in cosmeceuticals. The interactions between cosmeceuticals and skin are complex, depending on the specific composites in cosmeceutical products, condition of the skin or general health status of a subject, and the environment where the action occurs. As such, careful preclinical or clinical evaluation of efficacy and safety is a prerequisite for the development of a specific cosmeceutical product. This article reviews some of the ingredients that are currently in use or might be potential candidates in cosmeceuticals of different categories.

Introduction
The term cosmeceutical was first introduced by Albert Kligman<sup>1</sup> during a meeting about 20 years ago. It is a category of cosmetic products claimed to have biologically active ingredients with medicinal or druglike benefits. Furthermore, they satisfy the needs of beauty and health. Many substances, either chemically synthesized or extracted from plants or animals, can be used as functional ingredients. Nowadays, many cosmetic products with biologically active ingredients have been developed and marketed, though there are discrepancies about their regulations and approvals by the government.<sup>2</sup>

Cosmeceuticals are intended to carry out their functions as protection, whitening, tanning, antiwrinkling, deodorants, antiaging, and nail and hair care. Cosmeceuticals may, however, cause some unwanted problems. The common ones are irritability to the skin, contact dermatitis, photosensitivity, comedogenicity, hair and nail damage, hyper- or hypopigmentation, infectivity, carcinogenicity, and even systemic adverse effects. The research and development of cosmeceuticals, especially the composite active ingredients, should be based on their clarified sources, structures, interactive mechanisms with the skin, and, most importantly, their efficacy and safety on the targeted components of skin. Here we review some of the cosmeceuticals with different categories of functions, with special focuses on their biologically active ingredients.

Skin-whitening and/or depigmenting cosmeceuticals

The number and amount of melanocytes, as well as the type and distribution of melanin in the skin, are the main factors to determine the color of skin. The synthesis of melanin pigment is completed by a series of oxidative reactions, along which tyrosinase is the key enzyme.
Tyrosinase converts tyrosine to dihydroxyphenylalanine (DOPA) and then to dopaquinone; dopaquinone autoxidates to dopachrome and, finally, to dihydroxyindole or dihydroxyindole-2-carboxylic acid to form eumelanin (black-brown pigment). Dopaquinone can also be converted to cysteinyl DOPA or glutathione DOPA and subsequently form pheomelanin (yellow-red pigment). The etiology of hyperpigmentation includes postinflammatory hyperpigmentation, pregnancy, drugs, photosensitizing agents, UV light, or systemic diseases (eg, Addison’s disease, liver disease, pituitary tumors). There are many pigmentary disorders that pose cosmetic problems in humans. Melasma, freckles, and aging spots are among the most common ones.3

Hydroquinone, with a phenol structure, is well known for its suppressive effect on melanin synthesis. Topical hydroquinone in 2% to 4% concentrations, alone or in combination with tretinoin 0.05% to 0.1%, has been successfully used for years in treating melasma.4 The problem with hydroquinone use is that it can be a skin irritant causing contact dermatitis, particularly in higher concentrations of 4% or greater, or when combined with tretinoin. Hydroquinone is also an unstable and easily oxidized ingredient in cosmetic formulations. It is, therefore, essential to package it in a nontransparent and airtight container to avoid light and air exposure. An uncommon adverse effect is exogenous ochronosis, characterized by progressive sooty darkening of the skin area exposed to hydroquinone. Derivatives of hydroquinone have also shown some promises for lightening skin. For example, arbutin contains a form of hydroquinone (β-D-glucopyranoside) derived from the leaves of bearberry, cranberry, mulberry, or blueberry shrubs, and in most types of pears. Pure forms of arbutin derivatives, such as α-arbutin, β-arbutin, and deoxyarbutin, are considered more potent for lightening skin. It was reported that deoxyarbutin effectively inhibits mushroom tyrosinase in vitro with a Ki that is 10-fold lower than hydroquinone and 350-fold lower than arbutin. In a human clinical trial, topical treatment of deoxyarbutin for 12 weeks resulted in a significant or slight reduction in overall skin lightness and improvement of solar lentigines in a population of light skin or dark skin individuals, respectively.5 Arbutin inhibits melanin synthesis in a dose-dependent manner.6 So far, most of the research describing arbutin’s effectiveness has been done in vitro. Clinical studies are needed to test at what concentration or in what vehicle arbutin is more effective to lighten the skin, and what possible hazards it may pose to skin.7 Another study screened several phenolic derivatives using B16 melanoma cells and found that a biphenyl derivative, 2,2′-dihydroxy-5,5′-dipropyl-biphenyl (DDB), down-regulated melanin synthesis effectively. DDB down-regulates melanin synthesis by inhibiting the maturation of tyrosinase, leading to acceleration of tyrosinase degradation.8 DDB, thus, might be a potential depigmenting candidate as a cosmeceutical, given careful and sufficient testing and trials.

There are many forms and various sources of α hydroxy acids (AHAs), such as lactic acid, glycolic acid, malic acid, citric acid, mixed fruit acid, triple fruit acid, sugar cane extract, and so on. Primarily, lactic acid and glycolic acid are the most widely studied forms of AHAs because they have a molecular size that allows effective penetration into the top layers of skin. x Hydroxy acids have been used for years in chemical peels. It is generally assumed that AHAs at concentrations of 4% to 15% are not effective for inhibiting melanin production. Rather, it is believed that they can accelerate cell turnover rates and exfoliate the stratum corneum. Other research, however, has shown that lactic and glycolic acids can indeed inhibit melanin production in addition to their actions as an exfoliant on skin.9 There are reports that glycolic acid, or glycolic acid with hydroquinone, is highly effective in reducing the pigment in melasma patients.10 There have been, however, accumulating reports on adverse effects of cosmetics containing AHA. They include severe redness, swelling, blistering, burning, itching, discoloration, and increased photosensitivity. The side effects are related to the pH and concentration of AHA, vehicles used, and frequency of application.

Kojic acid (5-hydroxy-4-pyran-4-one-2-methyl), a natural substance produced by fungi or bacteria, such as Aspergillus, Penicillium, or Acetobacter spp, is present in traditional Japanese fermented foods. There is convincing evidence, in vitro and in vivo, showing kojic acid to be effective for inhibiting melanin production.11,12 Kojic acid is highly effective in reducing the pigment in melasma patients.13 The problem with kojic acid is that it is an extremely unstable ingredient in cosmetic formulations. Upon exposure to air or sunlight, it can turn to a strange shade of brown and lose its efficacy. Furthermore, some controversial studies have shown that kojic acid has some mutagenic properties, at least in some strains of bacteria.12,13 A stable derivative of kojic acid, 5-[(3-aminopropyl)phosphinoxy]-2-(hydroxy-methyl)-4H-pyran-4-one (Kojyl-APPA), was synthesized. Kojyl-APPA significantly inhibited tyrosinase activity at 24 hours after treatment in normal human melanocytes. In addition, Kojyl-APPA decreased melanin content to 75% of control in melanoma cells and decreased the newly synthesized melanin to 43% of control in normal human melanocytes. Its permeation through skin increased by about 8 times as compared with kojic acid.14 Again, there have been no reports on its clinical usefulness and safety issues.

Azelaic acid is a naturally occurring saturated dicarboxylic acid originally isolated from Pityrosporum ovale. It is an effective therapeutic agent in treatment of a number of skin disorders (eg, acne and rosacea) when applied in a cream or gel at concentrations of 15% to 20%. It can also inhibit melanin production. A double-blind study with 329 women showed that 20% azelaic acid cream in conjunction with a broad-spectrum sunscreen yielded 65% good or excellent results against melasma. Over the treatment period of 24 weeks, the azelaic acid cream had comparable effects to 4% hydroquinone cream with regard to overall rating, reduction in lesion size, and pigment intensity. Severe side effects such as allergic sensitization were not observed.

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with azelaic acid. Additional research, however, suggests that azelaic acid is more irritating than hydroquinone mixed with glycolic acid (source, eMedicine Journal, http://www.emedicine.com/, November 5, 2001). Nevertheless, azelaic acid is an optional candidate for skin lightening if a patient has acne and postinflammatory hyperpigmentation or has allergic reaction with hydroquinone.

Retinoids are compounds that have the basic core structure of vitamin A and its oxidized metabolites, or synthetic compounds that share similar mechanisms of action as naturally occurring retinoids. Topical retinoids such as all-trans-retinoic acid (RA), 13-cis-retinoic acid (isoretinoin), retinol, retinaldehyde, tazarotene, and adapalene have been shown to improve dyspigmentation of photodamaged skin, including mottling and actinic lentigines. All-trans-retinoic acid has been demonstrated to improve melasma and postinflammatory hypermelanosis. Furthermore, RA, in combination with hydroquinone or 4-hydroxyanisole, or azelaic acid increases the potency of depigmenting agents for the treatment of melasma, actinic lentigines, and postinflammatory hypermelanosis. There are several possible mechanisms underlying these effects. All-trans-retinoic acid inhibits melanin synthesis through down-regulation of tyrosinase and tyrosinase-related protein 1 expression in melanocytes. All-trans-retinoic acid could also act as a selective melanocytotoxin in relatively high doses. In addition, RA increases keratinocyte turnover and augments melanin loss from the epidermis. The inhibition of glutathione S-transferase by RA explains its synergistic depigmenting action in other melanocytotoxins such as hydroquinone. Topical retinoids could irritate the skin causing redness, dryness, swelling, desquamation, and subjective feelings such as itching, stinging, and burning sensation.

A pomegranate extract (PE) from the rind containing 90% ellagic acid showed inhibitory activity against mushroom tyrosinase in vitro, and the inhibition by the extract was comparable with that of arbutin. Orally taken PE also inhibited UV-induced skin pigmentation on the back of brownish guinea pigs. The intensity of the skin-whitening effect was similar between guinea pigs fed with PE and those fed with L-ascorbic acid. Pomegranate extract reduced the number of DOPA-positive melanocytes in the epidermis of UV-irradiated guinea pigs, but L-ascorbic acid did not. These results suggest that the skin-whitening effect of PE was probably due to inhibition of the proliferation of melanocytes and melanin synthesis by tyrosinase. Further clinical studies are needed to test its efficacy and safety.

Glabridin was extracted from licorice. It could inhibit tyrosinase activity of melanocytes without cytotoxicity, and it also inhibited UV-B–induced pigmentation and erythema by topical application in a 0.5% concentration. There are also more potent ingredients extracted from licorice that may become potential depigmenting agents. They include glabrene, isoliquiritigenin, glycyrrhizoflavone, and glyasperin; all of them could inhibit tyrosinase activity with different power.

Magnesium-L-ascorbyl-2-phosphate (MAP) is a stable derivative of ascorbic acid. When used as a 10% cream, MAP showed significant lightening effect in more than half of patients with melasma and solar lentigines. Furthermore, MAP has been shown to have a protective effect against skin damage induced by UV-B irradiation.

Alkyl esters of the natural product gentisic acid are also tyrosinase inhibitors. The smaller esters (eg, methyl and ethyl) were more effective. Sphingosylphosphorylcholine is emerging as a potent signaling-lipid mediator. It significantly inhibits melanin synthesis in a concentration-dependent manner, and further, that it reduces the activity of tyrosinase.

Some amides obtained from coupling p-hydroxycinnamic acid derivatives with phenylalkylamines were also very potent in inhibiting melanin synthesis. The most active amides were trans-N-caffeoyltyramine, N-dihydrocaffeoyltyramine, and trans-N-dihydro-p-hydroxycinnamoyltyramine. There have been no studies on what other effects these amides have on melanocytes, apart from their strong tyrosinase inhibition activities.

Melanin content of the cells was significantly decreased by C(2)-ceramide. The tyrosinase activity of cell extracts was reduced by C(2)-ceramide treatment. In the cell-free system, however, C(2)-ceramide could not suppress tyrosinase, whereas kojic acid directly inhibited tyrosinase. These results suggest that C(2)-ceramide decreases the pigmentation of melanocytes indirectly by regulating tyrosinase. Furthermore, C(2)-ceramide decreased the protein expression of microphthalmia-associated transcription factor, which is required for tyrosinase expression.

Zinc α-2-glycoprotein inhibits melanin production by B16 melanoma cells via posttranscriptional effects on tyrosinase protein. Because zinc α-2-glycoprotein is normally produced by epidermal keratinocytes, these studies raise the possibility that epidermal-derived zinc α-2-glycoprotein may play a part in normal regulation of melanin production in vivo. It is interesting to note that endogenous substances might be a potential candidate in a cosmeceutical.

Moisturizing cosmeceuticals

The stratum corneum is composed mainly of lipids, proteins, enzymes, and water. The extracellular lipid membrane of the stratum corneum is composed mainly of ceramides and its derivatives (40%), cholesterol (25%), and free fatty acids (10%-15%), followed by smaller amounts of triglycerides, stearyl esters, and cholesterol sulfate. These lipids are synthesized throughout the epidermis where they are packaged in lamellar granules and subsequently undergo differentiation and constitute the water barrier. Many factors could disturb their synthesis pathway, such as essential fatty acid deficiency, enzyme inhibitors, defective enzymes, enzyme deficiency, environmental constituents, topically

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applied agents, or water content of the stratum corneum. High amounts of cholesteryl sulfate, the intercellular cement, have been shown to inhibit desquamation. Cornified cell envelope, a structure synthesized at late stages of keratinocyte differentiation, is composed of structural proteins, including involucrin, loricin, and the small proline-rich proteins. The stratum corneum possesses approximately 30% water, which is mainly associated with its elasticity. A healthy stratum corneum contains about 10% tightly held water. The tightly bound water is closely dependent on the presence of natural moisturizing factor. Natural moisturizing factor is found exclusively in the cells. Perturbation of the aforementioned filaggrin. Natural moisturizing factor is composed of amino acids and their metabolites, which are byproducts formed from the breakdown of filagrin. Natural moisturizing factor is found exclusively inside the cells. Perturbation of the aforementioned composites in stratum corneum might cause functional defect and clinical symptoms. Dry skin is one of the common problems due to defective stratum corneum. It is a condition featured by some subjective or objective denominators, including sensory characteristics with dry, uncomfortable, itchy, stinging, and tingling sensation; tactile characteristics with a rough, uneven, and sandlike feeling; and visible characteristics with redness, lackluster surface, dry, white patches, flaky appearance, cracks, and even fissures. In addition, several skin diseases are also featured by dry skin, including atopic dermatitis, ichthyosis, and the like. Moisturizers are agents designed to repair the damaged stratum corneum to make the stratum corneum softer and more pliant by increasing its hydration, resulting in smooth, more supple, and healthier looking skin. Moreover, moisturizers are also designed to act as adjuvant treatment option for some dermatologic diseases with feature of dry skin. From the view of safety, therapeutic moisturizers should be noncomedogenic, devoid of irritant ingredients, and compatible with many other therapeutic regimens.

A formulation of lactic acid 12% neutralized with ammonium hydroxide and pramoxine hydrochloride 1% was tested on dry itchy skin for 7 days. Patients had statistically significant improvement in skin surface hydration by day 3, with further improvement by day 7, as compared with control. Pantothenic acid, a component of coenzyme A, serves as a cofactor for a variety of enzyme-catalyzed reactions that are important in the metabolism of carbohydrates, fatty acids, proteins, sterols, steroid hormones, and porphyrins. The topical use of dexamethasone, the stable aldehyde analog of pantothenic acid, improved stratum corneum hydration, reduced transepidermal water loss, and maintained skin softness and elasticity.

A ceramide-dominant physiologic lipid-based emollient showed satisfactory results in the treatment of childhood atopic dermatitis, which is featured by dry skin. A nicotinamide cream containing 2% nicotinamide was tested on atopic dry skin over 4 or 8 weeks; white petrolatum was used as control. The results showed that nicotinamide significantly decreased transepidermal water loss, but white petrolatum did not show any significant effect, though nicotinamide and white petrolatum increased stratum corneum hydration. Another study showed that a niacinamide-containing facial moisturizer improved the stratum corneum barrier and, thus, provided a clinical benefit to subjects with rosacea.

In xerotic skin, the proteolysis of desmosomes is reduced, leading to the accumulation of corneocytes on the surface of the skin. Soap-induced xerosis could be ameliorated by the topical application of exogenous protease, such as bovine pancreatic chymotrypsin, papain, and a bacterial protease from Bacillus licheniformis. Alcalase and optimase, both broad specificity alkali bacterial proteases, were the most efficient ones. Morphological and immunologic analysis of bacterial enzyme-treated skin revealed that topically applied protease specifically induced the degradation of the desmosomes, thereby promoting desquamation.

**Antiwrinkle cosmeceuticals**

Wrinkle is one of the key features of aging skin, including photaging and chronological aging. The exact pathogenesis of wrinkle is not fully understood yet. Changes in the dermis are most prominent in aged skin. Aged dermis has fragmented elastic fibers, decreased collagen, and disproportionate types I and III collagens. At the bottom of a wrinkle, type IV collagen is decreased. Glycosaminoglycans, especially hyaluronic acid, are decreased. Collagen damage is attributed to several types of collagen-degrading enzymes known as matrix metalloproteinases (MMPs). Metalloproteinases activation can result in production of collagenase, gelatinase, and stromelysin. The degradation of elastins might also be caused by MMP-2.

Paeoniflorin (PF), partially purified from roots of Paeonia lactiflora, protected cells from DNA damage induced by UV-B irradiation in cultured normal human keratinocytes and hairless mouse keratinocytes. It was also revealed that 0.5% PF-containing formulation reduced facial wrinkles during an 8-week clinical trial. These results suggest that the partially purified PF has potent antiaging and antiwrinkle activities, and should be a useful ingredient for these purposes.

It was found that Morinda citrifolia fruit extract up-regulated biosynthesis of type I collagen and glycosaminoglycans in primary cultures of normal human fibroblasts. 1,4-Dihydroxy-2-methoxy-7-methylanthraquinone, an active ingredient with a type I collagen–stimulating effect, was isolated and identified from M. citrifolia fruit. It was revealed that anthraquinone showed significantly increased elaboration of type I procollagen C-terminal peptide and glycosaminoglycans, and reduced expression of the collagenase MMP-1 dose dependently in human dermal fibroblasts. Furthermore, a nanoemulsion containing anthraquinone predominantly increased the dermal type I procollagen in
nude mouse skin. These results suggest that anthraquinone derived from *M. citrifolia* fruit extract is a good candidate for a novel antiwrinkle agent.40

The inner shell of the chestnut has been used as an antiwrinkle or skin-firming agent in East Asia. A 70% ethanol extract from this plant can prevent cell detachment of skin fibroblasts from culture plates, possibly through enhancing the expression of the cell-associated fibronectin and vitronectin. Scoparone (6,7-dimethoxycoumarin), isolated from the extract of inner shell of the chestnut, possessed similar properties. These findings underline the usefulness of these substances as antiwrinkle/skin-firming agents.41

Dimethylaminoethanol (DMAE) is an analog of the B vitamin choline and is a precursor of acetylcholine. In a randomized clinical study, 3% DMAE facial gel applied daily for 16 weeks has been shown to be safe and efficacious in the mitigation of forehead lines and periorbital fine wrinkles, and in improving lip shape and fullness and the overall appearance of aging skin. Application was well tolerated; an open-label extension of the trial showed that the long-term application of DMAE gel for up to 1 year was associated with a good safety profile. The benefits of DMAE may include a potential anti-inflammatory effect and an increase in skin firmness with possible improvement in underlying facial muscle tone.42

Ubiquinone (coenzyme 10) is present in almost all cells and is a precursor of acetylcholine. In a study involving human fibroblasts induced shortening of the cellular life span with dryness, scaling, and erythema.49 Alitretinoin (9-cis-retinoic acid) is a naturally occurring endogenous retinoid. It has the ability to bind and activate all known intracellular retinoic acid receptors, which might promote the repair mechanisms in damaged skin. A small-scale clinical trial showed that topical alitretinoin gel 0.1% was well tolerated by participants and showed improvement of benign skin lesions (eg, seborrheic keratoses) and precancerous lesions.

There are 2 distinct types of aging. One is intrinsic aging, which is the natural aging process. The other is extrinsic aging, which is caused by environmental factors such as repetitive facial expressions, gravity, sleeping positions, smoking, and, above all, exposure to the sunlight. The commonly seen features of intrinsic aging are fine wrinkles, thin and transparent skin, hollowed cheeks and eye sockets, loss of firmness on the hands and neck, sagging, dry skin that may itch, inability to sweat sufficiently, greying hair that eventually turns white, and hair loss. Extrinsic factors, especially sun exposure, often act together with the normal aging process to cause skin aging prematurely. Photoaging is the term especially reserved to describe extrinsic aging caused by sun exposure. Photoaging is often featured by age spots, spider veins on the face, rough and leathery skin, fine wrinkles that disappear when stretched, loose skin, a blotchy complexion, solar elastosis, actinic keratoses, and skin cancer. In photoaged skin, the epidermis has thinning of stratum spinosum and flattening of the dermoepidermal junction. Decrease in the numbers of melanocytes and dysregulation of melanocyte density result in guttate hypomelanosis and a blotchy complexion. The number of Langerhans cells also decreases, and the cells have less dendrites. There are thickened, tangled, and degraded nonfunctional fibers in the dermis.45 The interaction between collagen fibers and fibroblast is also decreased.46 In an experimental study, chronic UV-A irradiation of normal human fibroblasts induced shortening of the cellular life span and an increase of cellular diameter; MMP-1 was over-expressed after repeated UV-A irradiation.47

Photoaged skin has variable manifestations produced by changes of different cellular or noncellular components of the skin and caused by different mechanisms. It is difficult to invent a cosmeceutical with multifunctions to meet all the needs. Some of the aforementioned cosmeceuticals, such as depigmenting, moisturizing, and antiwrinkle cosmeceuticals, have the potency to relieve part of photoaging signs. The following describes some agents that might be of potential antiphotoaging properties.

Sesamol is a highly acclaimed antioxidant. An experiment on mouse skin showed that it has a good effect on prevention of photodamage, observed on biochemical and histopathologic changes.48

Several topically applied retinoids, such as tretinoin, isoretinoin, retinaldehyde, and tazarotene, have been proven clinically and histologically effective for treating the appearance of photoaging. Adverse effects are also documented as irritant reaction of variable intensity presenting with dryness, scaling, and erythema.49 Alitretinoin (9-cis-retinoic acid) is a naturally occurring endogenous retinoid. It has the ability to bind and activate all known intracellular retinoic acid receptors, which might promote the repair mechanisms in damaged skin. A small-scale clinical trial showed that topical alitretinoin gel 0.1% was well tolerated by participants and showed improvement of benign skin lesions (eg, seborrheic keratoses) and precancerous lesions.
Large, blinded, controlled trials are needed to investigate the role of this novel retinoid in the treatment of photoaging.

Genistein is a soybean isoflavone with diverse biologic activities. It substantially inhibits skin carcinogenesis and cutaneous aging induced by UV light in mice and photo-damage in humans. The mechanisms of action involve protection of oxidatively and photodynamically damaged DNA, down-regulation of UV-B–activated signal transduction cascades, and antioxidant activities. Clinical trials are required to further substantiate its clinical applications.

A newly formulated vitamin C complex having 10% ascorbic acid (water soluble) and 7% tetrahexyldecyl ascorbate (lipid soluble) in an anhydrous polysilicone gel base was tested to one half of the face and the inactive polysilicone gel base to the opposite side. The effects were evaluated clinically and histologically. A statistically significant improvement of the vitamin C–treated side was seen in the decreased photoaging scores of the cheeks and the perioral area. Biopsies showed increased Grenz zone collagen, as well as increased staining for messenger RNA for type I collagen. No patients were found to have any evidence of irritation and inflammation during the 12-week trial.

Green tea polyphenol inhibits the activity of collagenase and increases collagen biosynthesis rate of human fibroblasts.

### Table 1

<table>
<thead>
<tr>
<th>Ingredients</th>
<th>Purported action</th>
<th>Source</th>
</tr>
</thead>
<tbody>
<tr>
<td>AHAs</td>
<td>Exfoliation and improving circulation</td>
<td>Fruit acids (glycolic acid, lactic acid, citric acid, titaic acid, pyruvic acid, maleic acid, etc)</td>
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<td>Allantoin</td>
<td>Soothing the skin</td>
<td>Comfrey root</td>
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<td>Aloe vera power</td>
<td>Softening the skin</td>
<td>Aloe vera</td>
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<td>Free radical scavengers and antioxidant</td>
<td>Plants and animals</td>
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<td>Antioxidant and anti-inflammation</td>
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It can also inhibit tyrosinase activity. It was interesting to note that after irradiation at 40 kGy by γ-ray, the abovementioned effects were all unregulated. It was interesting to note that after irradiation at 40 kGy by γ-ray, the abovementioned effects were all unregulated. 53 Green tea polyphenol or green tea could protect UV-induced DNA damage in a variety of cell types, including skin fibroblasts and keratinocytes. When green tea was taken orally, it also showed photoprotective effects manifested as low DNA damage of peripheral blood cells.54,55 Orally taken green tea or green tea polyphenols have mild adverse effects, such as excess gas, upset stomach, nausea, heartburn, abdominal pain, dizziness, headache, and muscle pain.56 Though it looks likely that green tea might be a suitable candidate for antiaging, so far, there have been no convincing reports on the evaluation of topical use of green tea or its derivatives on skin. It should be kept in mind that green tea polyphenols are highly unstable and easily oxidized in ambient environment. Formulary of green tea polyphenols as active ingredients in topicals, therefore, remains a challenge in the cosmeceutical industries.

N-Furfuryladenine is a cytokinin growth factor that can be obtained from a variety of sources, such as plants, parts of animals, and even human urine.57 In the presence of calcium, it could promote differentiation of human keratinocytes.58 It could also inhibit oxidative and glycoxidative protein damage in vitro, and Fenton reaction–mediated oxidative damage to DNA.59,60 Cosmetic products containing N(6)-F-furfuryladenine have been developed and marketed for a couple of years. A randomized, blinded, and controlled clinical trial is needed to evaluate its efficacy and safety.

Conclusions

The essence of innovative cosmeceuticals is their functional active ingredients. Hundreds of substances have been screened, synthesized, and tested (as exemplified in Table 1).2,16 and many have been included in commercially available products, for example, chamomile and soy. Prudent measures should be taken on clinical trials of cosmeceuticals because the interaction between skin and cosmeceuticals could be influenced by environmental factors as temperature, humidity, pollution, microbial, light, and so on. In addition, the desired functions of a cosmeceutical might require a coordinating action of multiple ingredients. Moreover, there are problematic skin conditions that might change the interactive pattern and outcome between cosmeceuticals and skin. Scientific clinical evaluation is a must for research, development, and application of cosmeceuticals.

References


