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Moisturizers

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INTRODUCTION

Dry and chapped skin is a very common problem both in healthy individuals and in patients with skin diseases. Dry skin might be connected to some inherited disorders relating to the structure and function of the epidermis (e.g., ichthyosis, atopic dermatitis) and may also be secondary to other diseases (e.g., diabetes or renal failure). Moreover, the condition can occur in response to an environment with low humidity and/or low temperature. Exposure to solvents, cutting fluids, surfactants, acids, and alkalis may also produce dryness.

Several features give the impression of dry skin (1–4). The visible and tactile characteristics mentioned below are judged both by the dermatologist and the affected person, while the sensory characteristics are perceived solely by the affected person:

1. Visible characteristics—redness, lackluster surface, dry, white patches, flaky appearance, cracks, and even fissures
2. Tactile characteristics—rough and uneven
3. Sensory characteristics—dry, uncomfortable, painful, itchy, stinging, and tingling sensation

The term ''dry skin'' is not generally accepted. Some relate it to the lack of water in the stratum corneum (SC), whereas others consider dry skin to belong to a group of disorders with a rough skin surface (5,6). It has not been conclusively shown that the water content of the stratum corneum is reduced in all dry skin conditions. For example, reduced water content has not been detected in the pruritic and dry-looking skin of patients with chronic renal failure (7) or in the clinically dry-looking skin of the elderly (8). There is also a discrepancy between the subjective self-assessment and the clinical assessment of the presence of dry skin (3,4). However, in other studies, a decreased water content of the SC has been found in elderly patients with xerosis (9,10) and in studies of winter xerotic skin the water content of the stratum corneum correlated inversely with clinical scores of dryness (1,2). Furthermore, the dry-looking skin of patients with atopic dermatitis and psoriasis is less hydrated and less capable of binding water than normal skin (8,11–15). In vitro studies have also confirmed that pathological stratum corneum from atopic and psoriatic patients is less capable of binding water than normal stratum corneum (14,16).

Products used for treatment or prevention of dry skin are called emollients or moisturizers. They are able to break the dry skin cycle and maintain the smoothness of the skin. The term ''emollient'' implies (from the Latin derivation) a material designed to soften the skin (i.e., a material that ''smooths'' the surface to the touch and makes it look smoother to the eye). The term ''moisturizer'' is often used synonymously with emollient, but moisturizers usually contain humectants, which hydrate the stratum corneum. In the present chapter, the term moisturizer will be used, but may also apply to creams without humectants.

Application of moisturizers to the skin induces tactile and visual changes of the skin surface. The ratio between oil and water is important, as well as the type of oil and the amount and type of other ingredients (emulsifiers, humectants, etc). The combination of substances influences the initial feel of the product, its spreading behavior on the skin, whether and how fast it is absorbed, and how the skin feels after its use. Water in the applied products has an immediate hydrating effect, due to penetration into the skin from their water phase (17). Other ingredients can also be absorbed into the skin, be metabolized, or disappear from the skin surface by evaporation or contact with other materials (18–21).

Recent studies indicate that moisturizers may have greater impact on the skin than is generally believed. Moisturizers affect the structure and barrier function not only of diseased skin, but also of skin that looks normal. The term ''cosmeceuticals,'' as proposed by Kligman, may be relevant to describe moisturizers that contain no recognized medicaments, but nonetheless have medicinal value (22).

The present chapter will give an overview of the structure and function of dry skin relating to the use of moisturizers.

MOISTURIZERS IN RELATION TO SKIN STRUCTURE AND WATER CONTENT

Roughness and scaling are visible features of clinically dry skin in patients with atopic dermatitis (3). Closer examination of these areas by scanning electron microscopy shows that the surface morphology is changed from a regular pattern to a coarser one, with broad, irregularly running furrows and loss of minor furrows (3). Likewise, in xerosis, increasing derangement of minor furrows and later also of major furrows can be observed (23). A more coarse and irregular skin surface pattern with larger squares is also found in recessive X-linked ichthyosis (24).

Moisturizers are expected to increase skin hydration and to modify the physical and chemical nature of the surface to one that is smooth, soft, and pliable. Smoothing of the surface can be observed immediately after application of a moisturizer as a result of the filling of spaces between partially desquamated skin flakes (25,26). The surface friction is also changed after application of moisturizers (27). Besides mixing with material already present on the surface, topically applied substances may enter into the skin and affect its surface structure and water content.

Using instrumental evaluation of the skin topography the influence of moisturizers on the skin structure has been addressed (25,28–33). The roughness parameters and the distance between furrows/peaks can describe changes in the hydration status (28–35). Dry skin tends to have a larger number of high peaks and a larger distance between the peaks than normal skin (33,34). Hydration of normal skin has been reported both to decrease (28,29,35) and to increase (30) the roughness parameters. Cook found the distance between the peaks to be smaller after hydration (35). A single application of moisturizers has been found to decrease the roughness parameters and reduce the distance between the furrows during the first 2 h (31). No change in the roughness but a decrease in the distance between the peaks was found after a 21-day treatment period in a study by Cook (34).

Water in the SC is associated with the hydrophilic parts of the intercellular lipids and with the keratin fibers in the corneocytes (14,36). The fibrous elements in the corneocytes have hydrophilic properties and also contain a water-soluble fraction that enhances their water-holding capacity (37–39). In the hydrated SC, three types of water with different molecular mobilities can be found. At a water content below 10%, the primary water is tightly bound, presumably to the polar sites of the proteins (14,40,41). When the degree of hydration exceeds 10%, the secondary water is hydrogen bonded around the protein-bound water, and above 40 to 50% the water resembles the bulk liquid (14,40,41). It is the secondary water that contributes to the plasticity of the SC (14,39). The amount of tightly

bound water, which does not seem to have any plasticizing effect, is almost the same in different types of pathological skin, whereas the amount of secondary water is much smaller in SC from psoriatic patients and from elderly persons with xerosis than in normal SC (14). For instance, in normal SC from glabrous skin the content is 38.2 mg/100 mg dry tissue, as compared with 31.7 mg in senile xerosis and 27.2 mg in psoriatic scales per 100 mg dry tissue (14). Prolonged exposure to water induces a pronounced swelling of the SC in the thickness dimension (42), with swollen corneocytes, and in the intercellular lamellar regions rough structures, water pools, and occasionally vesiclelike structures can be seen by means of freeze–fracture electron microscope (43). Proinflammatory substances are also released from the SC, which incites an inflammatory reaction (44) and increases blood flow in subclinically irritated skin (45).

Possible Roles for Humectants

Moisturizers often contain low-molecular-weight substances with water-attracting properties, called humectants. These substances are supposed to penetrate into the skin and increase the degree of hydration of the SC. In some vehicle-controlled clinical studies on dry and irritated skin, the improvements have been amplified by the content of humectants in the moisturizer (37,46–51).

A special blend of humectants can also be found naturally in the SC; it is called natural moisturizing factor (NMF) (52). NMF can make up about 15 to 20% of the total weight of the corneum and substances belonging to this group are amino acids, pyrollidone carboxylic acid (PCA), lactates, and urea (Table 1) (52,38). NMF is formed from the protein filaggrin and this formation is regulated by the moisture content in the SC (97). Extraction of NMF from the skin reduces the ability of the SC to bind water (38,39,53,54). Pyrrolidone carboxylic acid

Table 1 Composition of Natural Moisturizing Factor (NMF)

	(%)
Amino acids	40.0
Pyrrolidone carboxylic acid	12.0
Lactate	12.0
Urea	7.0
Na, Ca, K, Mg, phosphate, chloride	18.5
NH3, uric acid, glucosamine, creatinine	1.5
Rest unidentified	

Source: Ref. 52.

(PCA) occurs primarily in the SC in the form of its sodium salt at levels reaching about 3 to 4% (53).

A deficiency of NMF is linked to dry skin conditions. In ichthyosis vulgaris (55) and psoriasis (56), there is a virtual absence of NMF. The amino acid composition of SC samples from old people are altered in xerotic skin (10,57). There is a decrease in the amount of water-soluble amino acids in relation to the severity of xerosis, a finding that has been suggested to reflect decreased profilaggrin production (10). A reduced content of amino acids has also been observed in experimentally induced scaly skin (58). Furthermore, the SC in patients with severe ichthyosis vulgaris with a low surface hydration state has a lower amino acid content than normal SC (10). The content of urea both in the normal and affected SC of patients with atopic dermatitis is also substantially reduced (59). In addition, a significant relationship has been found between the moisture-binding ability and the PCA content of samples of SC (53).

The water-binding capacity at various humidities differs between humectants (Table 2). For example, the sodium salts of lactic acid and PCA appears to be higher than that of glycerin and sorbitol (60,61). Urea also has strong osmotic activity (62,63). As may be anticipated, the water-holding capacity of normal SC and of scales from psoriatic and ichthyotic patients is substantially increased after treatment with urea and glycerin preparations (13,29,46,64). Likewise, PCA attracts water and increases the degree of hydration of solvent-

Table 2 Moisture-Binding Ability of Humectants at Various Humidities

Humectant	31%	50%	52%	58–60%	76%	81%
Butylene glycol						38[e]
Glycerin	13[c] 11[b]	25[a]	26[b]	35–38[c,f]	67[b]	
Na-PCA	20[c] 17[b]	44[a]	45[b]	61–63[c,f]	210[b]	
Na-lactate	19[b]	56[a]	40[b]	66[f]	104[b]	
Panthenol	3[d]		11[d]		33[d]	
PCA	<1[c]			<1[c]		
Propylene glycol				32[f]		
Sorbitol		1[a]		10[f]		

Description of test conditions can be found in the original articles.

[a] Ref. 60.

[b] Ref. 61.

[c] Ref. 53.

[d] Ref. 67.

[e] Ref. 68.

[f] Ref. 69.

damaged guinea pig footpad corneum (37). However, which of these substances most efficiently increases the skin hydration is not known. Besides differences in water-binding capacity, their penetration characteristics are important for the effect. The amount of urea (65,66) and glycerin (28) absorbed into normal SC can be followed using a simple tape-stripping technique.

Although water is known to play an important role in maintaining skin suppleness and plasticity (70), the humectants in themselves may also affect its physical properties. For example, α-hydroxy acids and NMF increase skin elasticity (71–76) and stimulate the keratinocyte ceramide synthesis (77). Studies also indicate that if NMF is removed, water alone cannot restore elasticity (76).

Furthermore, humectants might influence the crystalline arrangement of the bilayer lipids (78). In dry skin, the proportion of lipids in the solid state may be increased, and putative moisturizers may then help to maintain the lipids in a liquid crystalline state at low relative humidity (78,79). Glycerin has been shown to interact with model lipids to maintain the liquid crystalline state even at low relative humidity (79,78). It has also been proposed that glycerin may aid the digestion of the superficial desmosomes in subjects with dry skin and thereby ameliorate dry flaky skin (80).

Possible Roles for Lipids

The lipid composition of the epidermis changes dramatically during epidermal differentiation (81,82). There is a marked decrease in phospholipids and an increase in fatty acids and ceramides (81,82). In the final stages of this differentiation, keratinocytes discharge lipid-containing granules—lamellar bodies—into the extracellular spaces in the upper granular layer, where they form intercellular membrane bilayers (Fig. 1) (36,82–84). This lamellar material greatly expands the intercellular compartment and constitutes about 5 to 10% of the total weight of human SC (85,86). The composition of these lipids is unusual and is important for the water-holding capacity of the SC (54,87–89). Exposure of the skin to solvents removes the structural lipids and produces a chapped and scaly appearance (54,88,90,91). Furthermore, lipid depletion enhances the susceptibility of water-soluble materials to be extracted by water (39,54,87). Unlike the lipids in all other biological membranes, those in the SC do not contain phospholipids, but are mainly composed of ceramides, sterols, and fatty acids (Table 3).

Application of lipids to the skin surface may increase skin hydration by several mechanisms. The most conventional one is occlusion, which implies a simple reduction of the loss of water from the outside of the skin. Common occlusive substances in moisturizers are lipids, for instance, petrolatum, beeswax, lanolin, and various oils. Although they reduce water loss (17,92), their effect may be diminished when combined with other ingredients in skin-care products (93,94). These lipids have long been considered to exert their effects on the skin

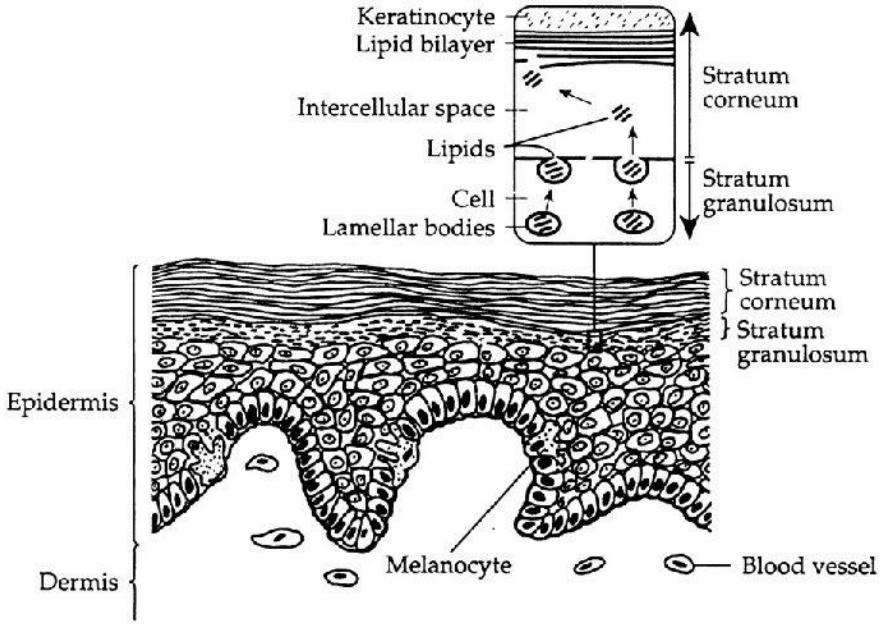

Figure 1 Structure of the epidermis and a schematic presentation of the formation of the intercellular lipid bilayer.

Table 3 Composition of Human SC Lipids

Lipid	Facial skin (Ref. 86)	Facial skin (Ref. 82)
Ceramides	19.9	39.1
Fatty acids	19.7	9.1
Triglycerides	13.5	0.0
Free sterols	17.3	26.9
Cholesteryl esters		10.0
Cholesteryl sulfate		1.9
Sterol/wax esters	6.2	
Squalene, *n*-alkanes	9.7	
Others	6.7	11.1

solely by forming an inert, epicutaneous, occlusive membrane. However, topically applied lipids penetrate the skin (21,95–103). For example, the syndrome of EFA deficiency is readily reversed by topical treatment with linoleic acid or sunflower seed oil, which is rich in linoleic acid (101–103). Furthermore, application of structural lipids from SC increases skin hydration and reduces scaling (89,104).

A more speculative mechanism behind the beneficial effects of lipids are their possible anti-inflammatory action. Polyunsaturated fatty acids in oils have been suggested to be transformed enzymatically by the epidermis into ''putative'' anti-inflammatory products (105). Treatment of UVB-induced acute inflammation shows that dietary supplementation with fish oil (106,107) and purified ethyl ester of eicosapentaenoic acid (20:5, n-3) from fish oil (108) has some anti-inflammatory effects. Topical (96,98), as well as oral (109), treatment with fish oils rich in omega-3 fatty acid is claimed to be effective against psoriasis, although this has been questioned (110–112). In patients with atopic eczema, no difference between fish oil and maize oil was detected in a double-blind multicenter study (113).

Atopic dermatitis has been reported to benefit from oral treatment with evening primrose oil, a vegetable oil rich in gamma linolenic acid (GLA), a fatty acid of the omega-6 family (114,115), although this has not been confirmed in other studies with topical (116) or oral treatment with evening primrose oil (117,118) or another oil rich in GLA—borage oil (119). Moreover, the GLA-containing borage oil is claimed to have good effect against infantile seborrheic dermatitis (99,100). The biochemical mechanisms of the possible therapeutic effects remain unclear, but it has been suggested that the enzyme δ-6-desaturase, which converts linoleic acid into GLA, might play a role, since it has been suggested that this enzyme is less active in atopic eczema and seborrheic dermatitis (99,120).

MOISTURIZERS IN RELATION TO THE BARRIER FUNCTION

Dry, scaly skin is usually associated with impaired barrier function (8,58,103,121–123). Impairment in the barrier function might be due to cracks in the skin, resulting from a decreased softness and flexibility of the SC (39,70). The projected size of the flattened corneocytes is also considered to influence the barrier function, and in dry, scaly skin the projected size is reduced, indicating a shorter penetration pathway through the skin (1,58,124). Furthermore, the lipid content and organization of these intercellular barrier lipids have broad implications for the permeability barrier function (36,83–85,125,126). The lipid composition of the SC is highly variable among individuals, depending on a number of factors (Table 4). In dry skin and in skin exposed to organic solvents, the lipid

Table 4 Factors Influencing the Lipid Composition of the Skin

Anatomical region (86)
Sex (136)
Age (136,137)
Season (137)
Exposure to surfactants (89,139)
Exposure to solvents (88,90,91,104)
Tape-induced scaly skin (58)
Atopic dermatitis (138,140–144)
Psoriasis (145)
Ichthyosis (146)
Essential fatty acid (EFA)-deficient states (103)

composition and normal bilayer structure are changed (58,88,90,91,104,127, 138,140–146). However, dryness of the SC may not necessarily increase skin permeability. For example, if the dryness is confined to the outermost SC layers and the major permeability barrier resides in the lower part of SC, no correlation between these parameters could be expected (89).

Improvement of the SC barrier function is central to the improvement of all dry skin conditions, in particular contact dermatitis and atopic dermatitis. Contact dermatitis is a major occupational skin disease and protective creams, also marketed as barrier creams or invisible gloves, have come to play an important role in protecting the skin from toxic substances. Protective creams are expected to be used on normal skin and form an impermeable film on the surface that can prevent noxious substances from entering into the skin. Such creams may also contain substances that trap or decompose the hazardous substance. Experimental studies also show that some creams can delay the contact with certain substances, whereas others enhance the penetration of the hazardous substance (128–133,147). Treatment can also reduce skin susceptibility to alkali, SLS, and DMSO, but increase absorption of hexyl nicotinate (134).

Considering the range of effects, the benefit of using protective creams in the prevention of contact dermatitis in industry or in wet working occupations is controversial (148). In a prospective study on metal workers, the beneficial effect from protective cream treatment was not confirmed, whereas an ordinary moisturizer decreased the prevalence of irritation (149). Moisturizers may also prevent contact dermatitis to a similar degree as barrier creams, but with the possible advantage of enhanced user acceptance (132,135).

In assessing the effects of moisturizers on skin barrier function (Table 5), studies evaluating the effects on diseased skin need to be distinguished from those

Table 5 Factors to Consider in Evaluating the Effects on Skin Barrier Function by Creams

Composition of the cream
Cream thickness; drying time
Test skin; animals or humans; normal or diseased
Single application versus repeated applications
Expected time course for effect
Biological endpoint
Challenging substance; application method; dosage

on normal skin (i.e., treatment or prevention). Furthermore, single or repeated treatment might be important for the outcome. One way to monitor changes in barrier function as a function of time is to measure TEWL (100,150–154). The level of TEWL has been suggested to serve as an indicator of the permeability of the skin to topically applied substances (155,156) and high basal values have also been found to predict increased skin susceptibility to chemical irritation stimuli (157–159).

Another method to assess the barrier function is to expose the living skin to substances with biological activity and to measure the response (Table 6) (132,133,160–165). However, long-term studies under real conditions are considered necessary to support the results from predictive testing (148,149).

Possible Roles for Humectants

In studies on dry skin, one might expect an improvement in the impaired skin barrier function in association with improvement of the clinical signs of dryness. TEWL has also been reduced in ichthyotic (46), atopic (163,166), and dry (167) skin by treatment with moisturizers containing humectants, such as urea or glycerin (46,166–169). In a placebo-controlled study, it has also been proven that urea

Table 6 Examples of Substances That Have Been Used to Test the Skin Barrier Function

Substance	Biological response	Refs.
Surfactants	Irritation	132, 133, 160, 158, 162, 163
Alkali resistance	Burning, itching, erythema	189, 161, 134
DMSO	Urticaria	190, 134
Nicotinates	Vasodilation	134, 165, 164, 185
Toluene	Irritation	133, 161

promotes barrier recovery in SLS-induced dry skin (170). However, a moisturizer without humectant (171) and another with ammonium lactate as humectant (32) had no effect on TEWL, despite clinical improvement.

Despite the widespread use of moisturizers, scant attention has been paid to their influence on the permeability barrier of normal skin. It may be anticipated that the use of moisturizers on normal skin will increase the permeability, since increased hydration of normal skin is known to reduce its diffusional resistance (172–175). Hydration may create interfacial defects in the lipid bilayer caused by phase separation (43,176). In vitro experiments on SC also indicate that humectants increase TEWL (61,92) and certain humectants are known as keratolytics (see Ref. 177 for an overview). However, studies in healthy volunteers show no increase in TEWL by repeated application of moisturizers, although the treatment appeared to increase the skin hydration significantly (162,178–180).

The use of moisturizers with urea has been questioned, with reference to the risk of reducing the chemical barrier function of the skin to toxic substances (62). Some single-application studies also show that urea may act as a penetration enhancer (164,181–185). However, not all studies support this belief (165,186,187) and repeated applications (10–20 days) of urea moisturizers on normal skin actually reduce TEWL (162,167,169).

In vivo TEWL measurements have also been combined with challenge of the skin with a vasodilator (nicotinates) and with an irritant [sodium lauryl sulfate (SLS)] to further elucidate changes in barrier function due to treatment with moisturizers (148,162,163,165,169,188). Single exposure to sodium lactate, sodium-PCA, and sorbitol show these to reduce the penetration of benzyl nicotinate (165). Furthermore, an increased resistance to SLS-induced irritation has been found after long-term treatment with urea (132,162,163,169), glycerin (132), and α-hydroxyacids (188). However, absence of effects has also been found for a moisturizer with glycerin (162) and, likewise, *increased* skin susceptibility to irritation has been shown after treatment with a moisturizer without any humectant (148).

B. Possible Roles for Lipids

A disturbance of the epidermal barrier function induces a rapid response of the keratinocytes to restore cutaneous homeostasis. The mRNA coding for proinflammatory cytokines, adhesion molecules, and growth factors is upregulated (191). Likewise, there is an increase in DNA synthesis, leading to epidermal hyperplasia, and in lipid synthesis (91,152,153,192–194). The synthetic activity includes unsaponifiable lipids (91,152,194), fatty acids (152), and sphingolipids (151). Sterols and fatty acids are synthesized immediately after barrier disruption, whereas the increase in sphingolipid synthesis is somewhat delayed (151). Over time, the content of lipids in the SC is restored to the normal level in parallel with the return of barrier function (91,151–153,193,194).

Topically applied lipids may also penetrate the skin and affect its barrier properties (90,99,100,103,126,154,195). For instance, sunflower oil, rich in linoleic acid, has been found to reduce abnormally high rates of TEWL in sodium-laurate-irritated rat skin (103) and borage-oil normalizes TEWL in infantile seborrheic dermatitis (99). Petrolatum has also been found to be absorbed into delipidized skin and to accelerate barrier recovery to water (154). In contrast to these findings, an inverse relationship was found between recovery of normal TEWL and the amount of sunflower seed oil in emulsions used for treatment of sodium lauryl sulfate (SLS)-induced irritation in humans (195). Moreover, applications of ceramides, linoleic acid, and a variety of other fatty acids alone delay barrier recovery in acetone-treated murine skin; likewise, two-component mixtures of fatty acid plus ceramide, cholesterol plus fatty acid, or cholesterol plus ceramide delay barrier recovery (90). The only treatments that allowed normal barrier recovery were applications of complete mixtures of ceramide, fatty acid and cholesterol, or pure cholesterol (90). Commercially available moisturizers have also been found to reduce elevated TEWL values in acetone-treated mice skin compared to untreated areas at various times during a 24-h test period (196). Furthermore, not only lipids but also emulsifiers can reduce TEWL in surfactant-irritated human skin (197). In normal forearm skin, a moisturizer without humectants has been found to increase skin susceptibility to SLS, without prior increase in TEWL (148).

DISCUSSION AND CONCLUSION

A lack of water may be too simple an explanation for all types of problems covered by the term dry skin, such as redness, scaling, roughness, itching, and a feeling of discomfort. Rather than just aiming at a general increase in the water content, the abnormal epidermis should probably be treated according to the underlying pathogenesis. The possibilities to correct or prevent abnormalities in the skin by different treatments may also help to explain the differences in preference for different moisturizers among individuals. This opens up new possibilities for further improvement in the treatment of different dry skin disorders.

The interesting findings that moisturizers also can affect barrier homeostasis clearly indicate that ingredients are not as inert to the skin as previously considered. A number of different mechanisms behind the barrier-improving effects from moisturizers have been suggested. It is obvious that a reduction in TEWL may be due to a simple deposition of lipid material to the surface, and not to any deeper effects in the skin. Another explanation is increased skin hydration, which increases SC elasticity and decreases the risks of cracks and fissures. Interference with the lipid layer around the corneocytes may also help to retain the moisture content in the corneocytes and prevent cracking of the SC (54,87–

89,104,154). Moreover, it is possible that the applied moisturizer decreases the proliferative activity of epidermis, which increases the size of the corneocytes. With a larger corneocyte area, the tortuous lipid pathway gives a longer distance for penetration, which reduces the permeability (58,124,198). Reduction in mitotic activity and cell proliferation has been found by treatment with lipids and urea (199–201).

Topically applied lipids may also penetrate deeper into the skin and interfere with endogenous lipid synthesis, which may promote, delay, or have no obvious influence on the normal barrier recovery in damaged skin (90,126). Furthermore, other substances in creams may influence the composition of the SC lipids (e.g., lactic acid has been found to stimulate the production of ceramides by keratinocytes in vitro) (77). Other mechanisms, such as anti-inflammatory actions, are also conceivable explanations to the beneficial actions of moisturizers on the skin.

Whether changes in TEWL are predictive also for the permeability to substances other than water is likely to be dependent on the mechanism for the change in TEWL. For example, TEWL may be reduced by absorption of certain substances from the moisturizer, but this may facilitate absorption of other exogenous substances into the skin.

In conclusion, we can foresee that the increased understanding of the interactions between topically applied substances and the epidermal biochemistry will improve the formulation of future skin care products (202). Furthermore, noninvasive bioengineering techniques will allow us to monitor treatment effects more closely and in the future we can also expect new devices that can diagnose specific skin abnormalities noninvasively.

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8
Botanical Extracts

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The existence of the word ''cosmeceuticals'' is very much linked to the U.S. FDA definition of drugs and cosmetics in the 1938 FD&C Act. One can only speculate as to why 60 years of scientific knowledge and research have been ignored by the FDA in not revising the definition! The European Commission has been wiser and its 1976 definition of cosmetics was modified in 1993 to acknowledge the fact that everything put on the skin or hair may have a physiological effect (1). It puts the responsibility on the industry to ascertain product safety and efficacy (claims justification) (2).

Natural extracts, whether from animal, botanical, or mineral origin, have been used as ''active ingredients'' of drugs or cosmetics for as long as human history can go. Oils, butter, honey, beeswax, lead, and lemon juice were common ingredients of the beauty recipes from ancient Egypt. Many botanical extracts are used today in traditional medicine and large pharmaceutical companies are rediscovering them.

The major differences between the drug and the cosmetic approach rely on the intent (i.e., ''cure or prevention of a disease'' vs. ''beautifying'') as well as how the extract is considered. In the cosmetic industry, the botanical extract *is* the active ingredient. It may contain hundreds of chemical structures and it has a proven activity. In the drug industry, you need to know the chemical structure of the active ingredient *within* the extract, very often to synthesize it, to purify it, sometimes to discover that isolation and purification leads to a loss in the biologi-

cal activity, or to realize that, despite all the skills of organic chemists, nature is *not* easy to reproduce.

ORIGIN OF BOTANICAL EXTRACTS

Botanical extracts have been used for centuries and are present in today's products either for their own properties or as substitute of animal materials that may have to be removed from products because pressure of animal rights associations or diseases like bovine spongiform encephalopathy (BSE). There are plant powders for hair coloring (Henne), scrubs (apricot kernel, corn), or masks (oat flour); plant extracts (''as is'' or purified); and biotechnology extracts obtained through fermentation, cloning, soilless culture (aquaculture, artificial media, etc.), which are developed from microorganisms, plant organs, total plants, or through the use of specific enzymes (3).

EXTRACTION PROCESS

Active ingredients ae not present in equal amounts in the plant or the organism. Most of the time, a higher concentration can be found in certain parts. Therefore, it is usually only one part of the plant that is used: fruit, bark, root, bud, flower, leaves, etc.

Depending on the future use of the extract, various extraction processes can be used. As mentioned, it is industry's responsibility to ensure the absence of toxic substances that could lead to unwanted side effects. The drug approval process allows side effects to be present provided the benefits outweight the disadvantages, while the cosmetics consumer has the choice of using a product that may have side effects or using another that has none, the product with side effects would not be acceptable.

Total Extracts

Total extracts are most common in the cosmetics industry, rarely, if ever, used in drugs. They are generally known from traditional usage, which has a long history. Their activity is often empirical and their active ingredients are not always identified, but their benefits are, very often, without possible doubt. Their mode of preparation can be found in traditional pharmacopeas (China, India, Africa, Europe, America), or from observing shamans or traditional practitioners. Very often, plants are blended in order to better control or synergize their effects, but sometimes also to preserve the secret of the active ingredient.

Modern techniques include: (a) pressing—for plants rich in water (e.g., juice, fresh plants, fruits, vegetables, cactus) or oil; (b) percolation, with one

solvent or a mixture of solvents (water, glycols, ethanol) at room temperature or at elevated temperature (this process is the same as the one used to obtain coffee); and (c) maceration, with the same type of solvents (this process is the same as the one used to obtain tea).

These processes allow for better controls: stability, preservation, manufacturing reproducibility.

The content of the extract is very much a function of the type of solvent, the temperature, the plant:solvent ratio, the time of contact, the part of the plant used and its species. Sometimes it is also dependent of the plant culture conditions and the season of harvest.

In the drug industry, especially, the extract must be concentrated and the active material isolated by selective precipitation, chromatography, electrophoresis, etc.

Solvents have to be carefully chosen, not only for their extraction properties, but also for their compatibility with the final formulation and their harmlessness.

Selective Extracts

Special extraction processes or the use of specific solvents will lead to the obtention of a specific class of molecules.

The fragrance industry has for centuries obtained essential oils or floral water by water vapor extraction or ''enfleurage''—a process by which the plant flowers are put in contact with solid fats and terpens and sesquiterpens migrate into the oil phase.

The use of vegetable oils as solvent allows for the extraction of oil-soluble vitamins or lipids. More recently the use of supercritic CO_2 has been developed to extract aroms, essential oils, and oleoresins.

Purification

Extract purification to separate specific molecules from others are done following classic physicochemical processes—cryoprecipitation, column chromatography, electrophoresis, use of selective solvents and salts, etc.

Biotechnology Extracts

Biotechnology can be used to obtain, purify, or transform extracts. The use of enzymes as tools in this area is booming (4). One can find different enzymes to be used for very specific reactions in certain conditions. They could become an alternative to chemical reactions as they provide stereospecificity or eliminate the risk of solvent residues. Today, protein hydrolysates obtained by enzymatic

reaction are free of the chlorine residues formed when acid hydrolysis is used. In addition, the use of exo-, endo-, or amino-acid-specific proteases allows for a better control of the end result.

Enzymes will allow for better yields by transforming or releasing specific molecules (use of pectinases, β-glucosidase, β-glucanase, lipases, transferases, esterases, etc.).

Amino acids, polyols, esters of fatty acids, polyol organic acids, more stable liposoluble vitamin esters with slow release properties, and new molecules (5) can be obtained.

Usage

Extracts or purified botanical molecules can be incorporated directly into solutions, emulsions, or vectors or can be used to form a vector (liposomes, phytosomes, phytospheres) (6). They can be topically applied, ingested, or injected, depending on the intended use and provided absence of toxicity has been shown.

Activity

Are botanical extracts really active? How does their activity compare to that of synthetic materials? Are all nautral ingredients safe?

Certainly one learns a lot on these questions by studying traditional uses. Centuries of human experience can prove safety. For example, lilium bulb oil extract use for sunburns has been reported since ancient Greece, while the water extract has been shown to be toxic. Natural ingredients have been shown to have a broad spectrum of activity, including hallucinogenic mushrooms and cardiotonic belladona. Scientific research conducted on plant extracts described in traditional pharmacopeas (7,8) has led to a broader range of potential applications.

Furthermore, research conducted during the last 10 years on skin biology allows us to better understand the biological mechanisms involved in dehydration, aging, etc. This, in turn, leads to the search for extracts with specific activities for targeted applications.

Antioxidants

Free radicals have been shown to play a major role in sun damage as well as in aging or in pollution (tobacco, stress). They act by degrading the skin structural fibers (collagen, elastin), cell membranes, DNA, or by creating inflammatory reactions (9). Free radical actions can be blocked by the following

Vegetable oils rich in tocopherols and tocotrienols. α-Tocopherol contributes directly to cell membrane structure by stabilizing it and allowing

for proper functioning of membrane enzymes. Wheat germ oil and palm oil are particularly rich in tocopherols and α-, β-, γ-tocotrienols.

Carotenoids, such as β-carotene, found in plants or in part of plants exposed to the sun. Of particular interest is a unicellular microalgae, *Dunaliella*. Under normal conditions of light, temperature, or salt, these algae are green. However, under extreme conditions (high salinity, low pH, high sunlight, lack of nitrogen or phosphorus), they protect themselves by multiplying their β-carotene concentration by 10. The ponds become red, and the β-carotene concentration can reach 14% of their dry weight.

As first shown by Kligman (10), the action of retinoids and carotenoids (11) on sun damage has led to numerous works.

SOD is an enzyme that deactivates free radicals. Its concentration decreases with age. It has been possible to obtain *Bifidus* extracts that are rich in SOD (12).

Ascorbic acid, which can be found in *Rosa canina* (dog rose) fruits, actinidia (kiwi fruits), or *Malphigia punicifolia* (West Indian cherry) is an antioxidant that is also used for many of its other properties.

It is active in the synthesis of carnitin, a molecule intervening in the transfer of lipids inside the mitochondria. Ascorbic acid thus plays a role in improving cell resistance due to a better use of lipids. Ascorbic acid is an anti-inflammatory agent that degrades and eliminates histamine. It can be used in after-sun products; it protects against free radical damage, helps maintain the elasticity and the integrity of the extracellular matrix (ECM), and has immunostimulating activity.

Flavonoids, rich extracts from *Gingko, Fagopyrum* (buckwheat), *Eucalyptus sambucus* (European elder), or *Sophora japonica* are used for their antioxidant and anti-free-radical properties (13).

Rosmarinus (rosemary) extracts, rich in carnosic acid, are very potent antioxidants, used to protect food.

Syzygium aromaticum or *Germanium thumbergii* extracts can be used to protect collagenase activity and ECM from free radicals (14).

Lipids of the Epidermis and Barrier Function

Fish oils rich in polyunsaturated fatty acids (PUFA) of the n-3 type [e.g., EPA (eicosapentaenoic acid) or DHA (docosapentaenoic acid)] act directly on cell membranes by increasing their fluidity. They favor the exchanges between the inner and the outer compartment of the cells or between cells. In addition, they have anti-inflammatory activity (15).

Thanks to the use of microalgae cultures in photobioreactors, plant oils rich in PUFA (EPA and DHA) can be produced.

Other plant oils rich in PUFA of the n-6 type [e.g., *Oenothera biennis* (evening primrose), *Borage officinalis* (borage), and *Ribes nigrum* (black currant)] are important in bringing essential fatty acids to the skin contributing to the maintenance or the restoration of epidermal lipids.

Oil and plant butters (rice, wheat, coffee, mango, sorgho, baobab, soya, corn, carob) are rich in essential fatty acids (EFA) (e.g., oleic and linoleic) or squalene (olive oil), which maintain skin suppleness and reduce water loss. They also contain a nonsaponifiable fraction rich in sterols. Some of these have exceptional healing properties that make them of particular value in sun or antiage products: *camelia* (tea), *argania, medicago* (alfalfa), *spinacia* (spinach), *Butyrospermomum* (shea butter), *Cucurbitaceae*, *Pongamia* (hongay or pongamia oil). β-sitosterol is well known for its inflammatory properties. The insaponifiable fraction is also a stimulant of collagen or elastin synthesis.

Phytosterols slow down the aging process by favoring fatty acid desaturation, which in turn maintains membrane fluidity and catalytic activity. γ-Orizanol (ferulic esters of cycloartanol, cycloartenol, and β-sitosterol) extracted from rice, topically applied, stimulates sebaceous gland activity, which slows down with age.

One can also find plant waxes (sugar cane, *Camauba*, *Ceroxylon*, *Jojoba*, rose) which are used to protect lips, hands, or face from dehydration.

Certain plants (yeast, wheat, apple, potatoes, rice bran, *Agaricus*, *Morus alba*, or white mulberry) are rich in ceramides and glycosylceramides. These may be used for their action on skin or hair to provide hydration or reconstitute epidermal barrier function.

Other plants are rich in oils containing very long-chain fatty acids (C22, 24, 26) like *Pentaclethra* or ewala oil used in Africa as a massage oil, or *Limnanthes alba* or shambrilla oil.

Fat Storage and Slimming

We are currently using botanical extracts with very specific actions that act at various levels of adipocyte metabolism.

Garcinia cambodgia decreases the transformation of sugars into fat.

Extracts of *Guarana*, tea, coffee, cocoa, which are rich in methylxanthines (caffeine, theobromin) are cAMP-phosphodiesterase inhibitors and thus accelerate lipid degradation.

Flavonoids, like quercetin or its derivatives, are also inhibitors of this enzyme and could lead to a 40% increase in cAMP.

Methylxanthins of the same plants will act on lipoprotein lipase (LPL), reducing the passage of fatty acids into the adipocyte.

Phytosterols from plant oils are being investigated for their potential action

on fat storage or degradation, on adipocyte differentation or multiplication.

Antiage

Ascorbic acid is a key element in collagen synthesis (also in ''botanical collagen''). It stimulates the production of RNA coding for collagen and contributes to the synthesis of hydroxyproline and hydroxylysine (which is responsible for collagen three-dimensional structure).

Tests on cells have shown that PCO (procyanidol oligomers) from pine barks or grape pits were active in reinforcing and protecting the structure of the ECM. They improve microcirculation leading to a better irrigation of the tissues and thus to nutrition, hydration, hormone transport, etc.

Protection of elastic fibers (collagens, elastin) is promoted by extracts having free-radical scavenging properties, activating the synthesis of these proteins or inhibiting the enzymes responsible for their degradation: *streptomyces*, black currant, *Centella asiatica* (rich in asiatic acid), *Rudbeckia purpurea, Coleus, Areca*, . . .

Apigenin, extracted from *Chamomile* and its derivatives, and rutin from *Fagopyrum* have anti-inflammatory properties (by inhibiting histamine release), but they are also β-glucuronidase inhibitors. They protect mucopolysaccharides from degradation. Other extracts rich in polyphenols—tanins—also have antihyaluronidase activity (16–18).

Amino acids obtained by biotechnology through the action of microorganisms or enzymes on plant extracts are used for stimulation of systems that are active in aging as well as slimming (arginin, glutamin, HGH), hair growth (glutamic acid), or immunity (arginin) (19,20). Recent studies show the importance of amino acids in protecting the skin barrier function.

Tryptophan (from *Spirulina*, soy bean, pumpkin), vitamin B3 (from *Saccharomyces*), vitamin B6 (from avocado, banana, yeast, wheat germ), calcium, or magnesium all stimulate melatonin (MSH) synthesis. This hormone is very important to many biological processes and decreases rapidly with age. Melatonin is present in animals as well as plants. The highest concentration is found in *Festuca*, oats, corn, rice, and ginger (21).

Alpha- or beta-hydroxyacids that have been in vogue in recent years, not only in cosmetics but also in OTC drugs, are common in the botanical world. Whether from fruits (e.g., bilberry, apple, lemon, orange, kalanchoe), *Tamarindus, Hibiscus*, sugar cane (*saccharum officinalis*), *Accer saccharum* (sugar maple), *Salix, Betula* (sweet birch), or *Gaultheria* (Wintergreen) (22), their efficacy has been shown in smoothing, brightening, and sloughing skin. They contribute to the elimination of dead cells from the skin surface, hydration, as well as cell renewal. These acids are broadly used in facial, body, and even scalp care.

Oligoelements and minerals like silicium can be found in *Equisetum* (Horsetail), *Oryza* (rice), or *Diatoma*. They contribute directly to the synthesis of collagen or proteoglycans and to the stabilization of ECM (23).

Selenium (*Astrogalus*) is said to play an important role in antiaging (immunity, inflammation, free radical scavenging), zinc (*Taraxacum*) in hair growth (action on testosterone) (24), and mother of pearl from shellfish in wound healing or tissue repair.

Saponins, a huge family of compounds, whether of a steroidal or triterpenic structure, are known for their detergent activity. They probably have other activities, which are yet to be established. Constant research shows that saponins, present in botanical extracts, have tremendous pharmacological and metabolic properties.

Ginseng and bupleurum—stimulate biosynthesis of proteins, RNA, cholesterol or lipogenesis.

Centella asiatica (asiaticosides)—stimulates synthesis of collagen and fibronectin.

Hedera, ficaria (hederagenin)—inhibits proteases.

Sterols from *sabal, serenoa as* well as $\Delta 7$ sterols are inhibitors of 5-α-reductase, an enzyme involved in androgenic alopecia, hyperseborrhea of the scalp or the skin, as well as acne.

Glycyrrhizin from *glycyrrhiza* and harpagosides from *harpagophytum* are broadly used for their anti-inflammatory properties.

Saponins have also been shown to increase stress resistance by increasing cortisol and prostaglandins, to protect membranes (*Eleutherococcus*), to increase metabolic efficacy (*Medicago*), to stimulate cells (*Ginseng, bupleurum*).

Extracts from *ganodema* are immunostimulating, immunoregulating, prolong all life in culture, and act on endocrine functions. They have been used in traditional Chinese medicine to slow down aging. This mushroom is rich in polysaccharides, triterpenes, and steroids.

Extracts from *arctophylos uva-ursi*, *coactis*, and *adenotricha* rich in arbutin and methylarbutin are used for their depigmenting effect. So are kojic acid, ascorbic acid and its derivatives, and SOD rich bifidus extracts. Rosmarinic acid from rosemary also has a tyrosinase-inhibiting activity.

CONCLUSION

Many other activities of botanical extracts have been shown and are used in cosmetics or drugs (OTC or traditional). The main difference between the two is really the intention of the manufacturer (i.e., cure or disease prevention rather

than improvement of overall condition of the skin or hair), by maintaining or improving the natural processes.

Most cosmetic products today address both the rational and the emotional aspects that characterize their need in society, while they are often still considered as a ''dream in a bottle'' (Charles Revson).

Botanicals are playing an increasingly important role in the activity and safety of cosmetics; they allow for a renewal of the source of active ingredients in drugs.

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