

# CHAPTER 1

## COSMECEUTICALS

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### 1.1 History and Background

Cosmeceuticals have become the fastest-growing segment of the personal care industry. About 25 years ago Dr. Albert Kligman of the University of Pennsylvania originally coined the term 'cosmeceutical', describing a hybrid category of products found on the spectrum between drugs and cosmetics that exert a pharmaceutical therapeutic benefit but not necessarily a biological therapeutic benefit.<sup>1</sup>

The difference between a drug and a cosmeceutical is that the former is defined by having a biological effect on living tissue. Another important distinction is that cosmeceuticals are not regulated by the U.S. Food and Drug Administration (FDA) and, thus, are not subject to premarket requirements for proof of safety or efficacy. Cosmeceutical products often are tested through *in vitro* studies using silicone replicas of skin and, at best, clinical trials are small, open-label studies usually supported by the cosmetic companies themselves. The rigorous testing required for pharmaceuticals is not mandatory for cosmeceutical products.<sup>2</sup>

There are approximately 400 cosmeceutical manufacturers, including companies that supply the cosmeceutical chemicals and/or manufacture the products in the U.S. market. The largest companies in the industry for

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finished products are Procter & Gamble, Johnson & Johnson, L'Oréal, Estée Lauder, Avon and Allergan, which together represent nearly one-half of the U.S. market.

### 1.1.1 Skin Protection

The efficacy of a cosmetic product depends not only on the active ingredients but also on the delivery system to improve its efficacy. We have to remember that skin is more than an assembly of several layers of cells as corneocytes, keratinocytes, fibroblasts and complementing each other. Chemical products, pollution, stress, irradiation from infrared (IR) and ultraviolet (UV) sources, and abrasion are involved in skin aging. The consequences can be visible or invisible: inflammation, burns, edema, long-term illness, actinic damage, and premature aging. The aging of the skin manifests itself in many ways: drying out, loss of elasticity and texture, thinning, damaged barrier function, appearance of spots, modification of surface line isotropy, and finally, wrinkles.

Most of the cosmeceuticals have been developed with claims of antiwrinkle and firming, moisturizing and lifting, skin toning and whitening activity; the antiaging category of skin care products shows presently the highest growth rates.

### 1.2 Regulations

In India, a well defined Drugs and Cosmetics Act (1940) operates the regulations of cosmetics under the authority of Central Drugs Standard Control Organization (CDSCO). For the manufacture of cosmetics for sale or distribution the manufacturer should build the factory premises according to the Schedule M-II. Rapid growth of Pharmaceutical Industry has revamped and modernized the regulatory set-up of the country. Many areas including the production and distribution of healthcare products are brought under the same ambit of regulatory framework. Bioproducts, food additives and medical devices are all been regulated by regulating committee. Conducive environment in India also encourages substantial growth in all departments. With the introduction of Patent Act 2005, many new manufacturers are able to patent their products and market them effectively. The new regulatory guidelines have facilitated Research and Development activities to ensure the standard and quality of new drugs. It has also given an opportunity for the new players to invest in the emerging market of drugs and cosmetics manufacturing. Market friendly changes in the policies have also boosted up the market of Pharmaceutical Industry.

According to Drugs and Cosmetics Act (1940), “cosmetic” means any article intended to be rubbed, poured, sprinkled or sprayed on, or introduced into, or otherwise applied to, the human body or any part thereof for cleansing, beautifying, promoting attractiveness, or altering the appearance, and includes any article intended for use as a component of cosmetic.

In 1938, the U.S. Congress enacted a statute that officially defined cosmetics and drugs in detailed terms, setting up formal criteria for classifying a product as either a drug or a cosmetic. No intermediate category exists, although it was appreciated that a topical could be both a cosmetic and a drug at the same time. This remains the law to this very day. It defined a cosmetic, in pertinent part, as an “article intended for beautifying and promoting attractiveness.” In contrast, a drug was defined as a substance for use in the diagnosis, cure, treatment, or prevention of disease, intended to affect the structure and function of the body. This last clause legally determines whether a formulation is a drug or a cosmetic. Most skin care products lie somewhere in between drugs and cosmetics.

They comprise a continuous spectrum of substances intermediate between the two polar categories defined by Congress. Some traditional cosmetics are more drugs like in their beneficial effects and some drugs impact principally on appearance. It is this intermediate, broad-spectrum range of substances that consists of both drugs and cosmetics which justifies the fusion term cosmeceuticals. This is simply a biological concept that recognizes the new realities of skin care products.<sup>3</sup> Cosmeceutical is a pragmatic term that enables us to state without pretense the benefits of a product. It is not an invitation to pass new laws. There are three main trading blocks, the United States, Europe, and Japan. Obviously globalization as an integrated free-trade network cannot work if each block classifies and regulates skin care products differently. Unfortunately, no international consensus currently exists, inevitably sparking disputes and trade practices that may place some producers at a grave disadvantage. The situation is more complex and far more demanding in Europe. This is made obvious in the European Economic Cosmetic (EEC) Directive of 1993. The requirements for labeling cosmetics are formidable and daunting.<sup>4</sup> The product information that must be made available to officials encompasses the following: qualitative and quantitative composition of the product; specifications of raw materials; methods of manufacture; safety assessments; and proof of effectiveness.

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In the United States, manufacturers are not required to demonstrate either safety or efficacy prior to marketing, as is the case for drugs. On top of all this, the EEC has prohibited testing on animals after January 1998. Japanese authorities have created their own laws in response to the problem that many skin care products are neither pure drugs nor pure cosmetics in the traditional sense, but mixtures of the two. The category we call cosmeceuticals they call 'quasi drugs.' They allow cosmetics to include pharmacologically active ingredients, provided that the medicinal effects are mild and the products have been demonstrated to be safe. The legal wording leaves a lot of room for ambiguities and ad hoc interpretations that some perceive as a trade restraint.

In the United States, the following agents are regulated as drugs while in Europe (according to the European commission on cosmetics) they are sold as cosmetics.

1. Antiperspirants
2. Antidandruff shampoos
3. Sunscreens

This classification is detrimental to industry in the United States, especially in the case of sunscreens, which are more advanced and more effective in Europe because there is greater choice of ingredients. Paradoxes also abound in the United States. For example, retinol (vitamin A) can be sold as a cosmetic, but its oxidation product, retinoic acid, is regulated as a drug. However, the product is still only available by prescription. On the other hand, minoxidil, a drug that purports to grow hair and improve attractiveness, satisfies the basic definition of a cosmetic and is available without a prescription. New insights about the function of the skin, as well as the development of new products for skin care, make it necessary to question or redefine the definitions of cosmetics and drugs. Moreover, in the United States, Europe, and Japan, different definitions of cosmetics are used. The definition of a drug is more or less equivocal on these countries.

According to the Food, Drug and Cosmetic (FDC) Act, a drug is defined as an article intended for use in the diagnosis, mitigation, treatment, or prevention of disease or intended to affect the structure or any function of the body. In the United States, according to the FDC act of 1938, a cosmetic is defined as an article intended to be rubbed, poured, sprinkled, or sprayed on, introduced into, or otherwise applied to the human body or any part thereof for cleansing, beautifying, promoting attractiveness, or altering the appearance without affecting structure or function.<sup>6</sup> It is noteworthy that in this definition the cosmetic is not

allowed to have any activity (i.e., without affecting structure or function). In Europe, the definition of a cosmetic was re-evaluated and described by the council directive 93/35/EEC of June 14<sup>th</sup>, 1993.<sup>7</sup> The cosmetics directive contains 15 articles. The definition of a cosmetic is described in article 1 and is as follows:

A ‘cosmetic product’ shall mean any substance or preparation intended to be placed in contact with the various external parts of the human body epidermis, hair system, nails, lips and external genital organs or with the teeth and the mucous membranes of the oral cavity with a view exclusively or mainly to cleaning them, perfuming them, changing their appearance and/or correcting body odours and/or protecting them or keeping them in good condition.

According to the pharmaceutical affairs law, the Japanese definition of a cosmetic is as follows:

The term cosmetic means any article intended to be used by means of rubbing, sprinkling or by similar application to the human body for cleansing, beautifying, promoting attractiveness and altering appearance of the human body, and for keeping the skin and hair healthy, provided that the action of the article on the human body is mild.

The Japanese definition is only slightly different from the definition of a cosmetic within Europe. Both definitions allow a cosmetic to have mild activity and possess pharmaceutical activity. This is in sharp contrast to the definition of a cosmetic in the United States. The introduction of the term ‘‘cosmeceutical’’ enables to classify more precisely a product with an activity that is intended to treat or prevent a (mild) skin (abnormality). In order to avoid introducing new definition criteria, cosmeceuticals are only regarded as a subclass within the domain of a cosmetic or drug. In Europe and Japan, cosmeceuticals can be regarded as a subclass of cosmetics; however, in the United States cosmeceuticals can only be regarded as a subclass of drugs. Cosmeceuticals could be characterized as follows:

1. The product has pharmaceutical activity and can be used on normal or near-normal skin.
2. The product should have a defined benefit for minor skin disorders (cosmetic indication).
3. As the skin disorder is mild the product should have a very low-risk profile (see Table 1.1).

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**Table 1.1** Cosmeceuticals as a Subclass of Cosmetics (Europe and Japan) and as a Subclass of Drugs (U.S.).

	<b>Cosmetic</b>	<b>Cosmeceutical</b>	<b>Drug</b>
Pharmaceutical activity	+	+	+
Intended effect in skin disease	-	+	+
Intended effect in mild skin disorder	-	+	+
Side effects	-	±	+

The procedure for registration of a cosmeceutical should not be as cumbersome as for drugs. The intended activity of the cosmeceutical for treatment of a minor skin disorder should be demonstrated by clinical studies within the framework of good clinical practice. Moreover, it should be shown that safety requirements are optimal and that no side effects can be expected.<sup>8</sup> The safety evaluation is mandatory for cosmetics in Europe, according to articles 2, 12, and 13. In the United States, this would mean that a subclass of drugs (cosmeceuticals) are registered in a similar manner as over-the-counter products.<sup>9</sup> It would be beneficial if these countries could agree on the definitions of cosmetics and drugs and, in so doing, define cosmeceuticals as a subclass of cosmetics. This would prevent the current situation in which certain products are registered as drugs in the United States (sunscreens) and as cosmetics or cosmeceuticals in Europe and Japan. Clearly cosmeceuticals are the fastest growing segment of the skin care market and are currently the driving force in the field of skin care research.

**Table 1.2** Summary of cosmetic regulations- USA, EU and INDIA<sup>10</sup>.

<b>CONTENTS</b>	<b>USA</b>	<b>EU</b>	<b>INDIA</b>
Authority	FDA	EMA	CDSCO
Rules and regulations	Food Drug and Cosmetic Act	Council Directive 76/768/EEC	Drugs and Cosmetic Act
Pre-market approval	Not required	Not required by Cosmetic Directive	Required under state govt. licensing
Labelling	Should comply with the FD&C and FP&L	Based on Council Directive 76/768/EEC	Should comply with part XV of the D&C rules 1945
Expiry date	No date required	Date of minimum durability if durability is <30 months. Period after opening if durability is >30 months	Indicated as 'use before date'
Post marketing reporting system	Yes (voluntary cosmetic registration programme)	N/A	N/A

**Table 1.3** Regulations specifically prohibit or restrict the use of the following ingredients in cosmetics<sup>11</sup>.

<b>Ingredient</b>	<b>Activity</b>
Bithionol	Because it may cause photo-contact sensitization.
Halogenated salicylanilides (di-, tri-, metabromsalan, and tetrachlorosalicylanilide)	Because they may cause photocontact sensitization.
Chloroform	Because of its animal carcinogenicity and likely hazard to human health.
Vinyl chloride	As an ingredient of aerosol products, because of its carcinogenicity
Zirconium-containing complexes	In aerosol cosmetic products, because of their toxic effect on lungs, including the formation of granulomas.
Methylene chloride	Because of its animal carcinogenicity and likely hazard to human health.
Chlorofluorocarbon propellants	The use of chlorofluorocarbon propellants (fully halogenated chlorofluoroalkanes) in cosmetic aerosol products intended for domestic consumption is prohibited.

### 1.3 Types of Cosmeceuticals

Based on their function cosmeceuticals are classified as follows-

- Skin-whitening and/or depigmenting cosmeceuticals
- Moisturizing cosmeceuticals
- Antiwrinkle cosmeceuticals
- Sunscreen cosmeceuticals
- Antiphotaging cosmeceuticals

Based on various products presently on the market, cosmeceuticals can be divided into the following broad categories:

- Antioxidants
- Growth factors
- Peptides
- Metals
- Anti-inflammatories/botanicals,
- Polysaccharides
- Pigmentlightening agents.

**1.3.1 Antioxidants<sup>12</sup>**

Oxidative stressors create inflammatory molecules that lead to the formation of free radicals species. These free radicals are highly reactive molecules with unpaired electrons, and they can cause cellular damage to cell membranes, lipids, proteins, and DNA. Damage to DNA eventually results in collagen breakdown. Free radicals also play a role in 3 additional detrimental processes: inflammation, photodamage, and carcinogenesis. Antioxidants neutralize damaging free radicals by quenching reactive molecules and, thus, protecting cells from both endogenous stress (by-products of cellular energy) and exogenous stressors (ultraviolet light, pollution, cigarette smoke).

Antioxidants comprised a group of diverse molecules including, but not limited to, vitamins (A, B, C, and E), alpha lipoic acid (ALA), Coenzyme Q-10 (CoQ-10), idebenone, polyphenols, and kinetin. They vary in their abilities to protect against inflammation, photodamage, and carcinogenesis.

**1.3.1.1 Vitamin A*****Forms***

Several forms of vitamin A are used cosmetically, in particular retinol, retinyl esters (e.g., the acetate, propionate, and palmitate esters of retinol), and retinaldehyde. Through endogenous enzymatic reactions, these are all ultimately converted to trans-retinoic acid, which is the functional form of vitamin A in skin.

***Mechanisms***

Interaction of trans-retinoic acid with nuclear receptor proteins leads to interaction with specific DNA sequences to affect transcription, resulting in either increased or decreased expression of specific proteins/enzymes. Among the many gene expression changes induced by retinoids, some specific ones that are likely relevant to skin antiaging effects are those leading to thicker skin, which likely contributes to diminish fine lines and wrinkle appearance, for example, increased epidermal proliferation and differentiation (epidermal thickness increase), increased production of epidermal ground substance (glycosaminoglycans [GAG] that bind water, thus increasing epidermal hydration and thickness), and increased production of extracellular dermal matrix components such as collagen (dermal thickness increase). In addition to stimulatory effects, retinoids also have inhibitory effects. For example, retinoids are reported to reduce production of collagenase and inhibit production of excess ground



substance in photoaged dermis, an important mechanism because reduction in excess GAG is associated with reduced skin wrinkling. Retinoids also reduce expression of tyrosinase, a key enzyme in the conversion of tyrosine to melanin. Because the epidermal effects of a topical retinoid such as trans-retinoic acid (e.g., epidermal thickening) occur within days after initiation of treatment, skin effects such as fine line reduction can begin to appear quickly. In general, retinoids are very potent, so topical doses of less than 1% are typically sufficient to obtain significant effects.

Working with retinoids presents two substantial challenges. The first is their tendency to induce skin irritation. Choice of retinoid can reduce this issue. Retinol is better tolerated by skin than trans-retinoic acid, 2-retinaldehyde has irritation potential similar to retinol and retinol esters are better tolerated than retinol. The second key concern is instability, especially in the presence of oxygen and light. To increase retinoid stability in finished product, formulation and packaging should ideally be done in an environment with minimal exposure to oxygen and light.

### **1.3.1.2 Vitamin B3**

#### ***Forms***

The primary forms of vitamin B3 that have been used in skin care products are niacinamide (nicotinamide), nicotinic acid, and nicotinate esters, such as tocopheryl nicotinate, myristoyl nicotinate, and benzyl nicotinate.

#### ***Mechanisms***

Vitamin B3 is an essential vitamin. It is a precursor to a family of endogenous enzyme cofactors, specifically nicotinamide adenine dinucleotide (NAD), its phosphorylated derivative NAD(P), and their reduced forms NAD(H) and NAD(PH), which have antioxidant properties. These cofactors participate in many enzymatic reactions in the skin and thus can potentially influence many skin processes. The diversity of processes in which these cofactors participate may be the mechanistic basis for the diversity of cosmetic effects observed from the topical use of a precursor such as niacinamide. Fairly high doses (2% to 5%) of vitamin B3 have been used to achieve these desired effects like improved skin color, skin barrier improvement, reducing skin sensitivity and responsiveness to environmental insult, such as from surfactant exposure.

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The key challenge for working with niacinamide and nicotinate esters is avoiding hydrolysis to nicotinic acid. Nicotinic acid, even at low doses, can induce an intense skin reddening (flushing response). Formulating in the pH range of 4 to 7 is preferred to avoid hydrolysis. Most of the esters, unfortunately, induce a skin flushing response, some within seconds or minutes of topical application even at very low concentrations of less than 1%. Some of the esters, such as tocopheryl nicotinate and myristoyl nicotinate, apparently are less prone to cause this flush response and thus appear to be more suitable for aesthetic use topically.

### 1.3.1.3 Panthenol

#### *Form*

Panthenol, or provitamin B5, is also known as pantothenol and pantothenyl alcohol. The D optical isomer of panthenol is termed dexpanthenol. It is a precursor to pantothenic acid (vitamin B5).

#### *Mechanisms*

Because panthenol is a precursor to pantothenic acid, its skin effects may derive from this precursor role. Pantothenic acid is a component of coenzyme A, which is critical in cellular metabolism, including in acyl group transfer during fatty acid biosynthesis and gluconeogenesis. By increasing synthesis of stratum corneum lipids, improved barrier could result. Panthenol also promotes fibroblast proliferation and epidermal reepithelialization in vitro, effects that might promote wound healing. Because panthenol is water soluble and hydroscopic, it has skin moisturization potential, especially when combined with the widely used moisturizing agent glycerol.

High temperatures must be avoided when formulating with D-panthenol, which is the active form of the material, to avoid conversion to DL-panthenol. The only other challenge in working with this water-soluble material can be product stickiness if high levels are used.

### 1.3.1.4 Vitamin C

#### *Forms*

There are many forms of this vitamin. Some commonly used ones are ascorbic acid, ascorbyl phosphate (magnesium or sodium salt), ascorbyl palmitate, and ascorbyl glucoside.

### *Mechanisms*

Vitamin C has been used as a skin lightener because of its antioxidant activity and tyrosinase inhibition effect. It has also been described as an anti-inflammatory agent because it reduces the erythema associated with postoperative laser resurfacing. In addition, ascorbic acid serves as an essential cofactor for the enzymes lysyl hydroxylase and prolyl hydroxylase, both of which are required for posttranslational processing in collagen (types I and III) biosynthesis. Thus, by stimulating these biosynthetic steps, ascorbic acid has potential to increase collagen production for wrinkle appearance reduction. Ascorbate compounds have been reported to have skin anti-aging effects in the topical doses range from 3% to 17%.

The primary challenge with vitamin C and derivatives is stability (oxygen sensitivity), particularly with ascorbic acid, where loss of nearly half of the ascorbic acid in a month can occur. This is accompanied by rapid product yellowing, which is likely an aesthetic negative for the consumer. Various stabilization strategies can be attempted to address the issue, such as exclusion of oxygen during formulation, oxygen-impermeable packaging, encapsulation, low pH, minimization of water, and inclusion of other antioxidants. Despite these strategies, ascorbate stability remains a challenge, and some of these approaches, such as very low pH, can lead to unwanted aesthetic skin effects. One family of ascorbic acid derivatives is the ascorbyl phosphate salts (Mg and Na). The stability of these salts is substantially better than for ascorbic acid. Another challenge is skin delivery. Penetration of ascorbic acid across skin is generally poor, and typically less than 1% of the topical dose enters the skin. For the phosphate derivatives of ascorbate, skin penetration can be an even greater challenge due to the negative charges on the phosphate moiety. Thus, the use of approaches to enhance skin penetration is desired.

#### **1.3.1.5 Vitamin E**

##### *Forms*

In addition to the more commonly used forms of vitamin E, in particular tocopherol and tocopheryl acetate, several other esters, for example, succinate, nicotinate, linoleate, and phosphate, are used in the cosmetic arena. Natural tocopherol also has several isomers (alpha, beta, gamma, and delta) that differ in some of the side chains and have somewhat different potency. The more cost-effective among these is synthetic alpha-tocopherol.

### *Mechanisms*

Vitamin E is an oil-soluble antioxidant. Because oxygen radicals are involved as a factor in many skin problems, both acute and chronic, vitamin E has the potential to prevent and improve skin problems caused by these radicals, in particular, those caused by UV exposure such as sunburn, skin photoaging (wrinkling), and hyperpigmentation. Topical vitamin E is effective in preventing UV-induced skin redness. Vitamin E, at relatively high doses, provides significant effects.

Because tocopherol and tocopheryl acetate are oil soluble, using high levels can present some challenge in developing an aesthetically elegant (nongreasy) formulation. There is some oxidative stability concern with tocopherol; thus, tocopheryl acetate is often used to avoid this issue. Tocopheryl acetate appears to be less effective, however, due to apparently slow hydrolysis to the functional free tocopherol.

#### **1.3.1.6 Alpha lipoic acid**

Alpha lipoic acid (ALA) is a lipoamide synthesized in the mitochondria of plants and animals. It is a scavenger of reactive oxygen species and a metal chelator. ALA regenerates endogenous antioxidants such as vitamins C and E, glutathione and ubiquinol. ALA is both water and lipid soluble, allowing it to penetrate lipophilic cell membranes and enter the aqueous intracellular matrix. The molecule prevents lipid peroxidation, has anti-inflammatory properties, and acts as an exfoliant. ALA does not protect against UV-induced erythema or reduce the number of sunburn cells.

#### **1.3.1.7 Ubiquinone**

CoQ-10, or ubiquinone, is a fat-soluble antioxidant located in the inner mitochondrial membrane of nearly all living cells that is necessary for steps in adenosine triphosphate (ATP) production for cellular energy. It acts by downregulating MMPs. CoQ-10 also inhibits lipid peroxidation in plasma cell membranes. There is good in vitro evidence that CoQ-10 can decrease periorbital wrinkles. Idebenone is a more potent synthetic analog of CoQ-10 that is a powerful antioxidant. Idebenone shows highest anti-inflammatory properties, photoprotective effects, and prevention of UV immunosuppression. It may repair mitochondrial DNA and decrease nuclear thymine dimer photoproducts. Like other antioxidants, idebenone downregulates MMP expression. Overall, it may improve roughness, dryness and fine lines, and increase hydration.

### 1.3.1.8 Polyphenols

Polyphenols are plant-derived antioxidants that have anti-inflammatory, photoprotective, and anticarcinogenic properties. Flavonoids are a subgroup of polyphenols that are popular ingredients in many cosmeceuticals. They include grape seed extract, green tea extracts, and soy isoflavones. Grape seed extract can induce vascular endothelial growth factor expression on keratinocytes to enhance dermal wound healing. Green tea extracts such as epigallocatechin 3-gallate have been shown to decrease levels of UVB damage, DNA damage, sunburn, and erythema.

### 1.3.2 Growth Factors

Growth factors comprise a large group of regulatory proteins that attach to cell surface receptors to mediate inter- and intracellular signaling pathways. Wound healing relies on a complex interaction of various cytokines and growth factors.

Growth factors relevant to wound healing may induce new collagen, elastin, and glycosaminoglycan formation and mediate angiogenesis.

One human growth factor presently used in cosmeceuticals is transforming growth factor-1, which is derived from cultured fibroblasts harvested from neonatal foreskin. Advances in biotechnology have led to further products such as processed skin cell proteins (PSPTM) harvested from fetal cell lines. Other growth factors include placental extract, recombinant epidermal growth factor, and platelet-derived growth factor.

### 1.3.3 Peptides

#### *Forms*

With variations in amino acid sequence, number of amino acids, and use of derivatives of these acids, the array of possible peptides is limitless. A few peptides with known sequences have been of particular interest to the cosmetic industry, such as palmitoyl-lysine-threonine-threonine-lysine-serine (pal-KTTKS; Matrixyl), acetyl-glutamate-glutamate-methionine-glutamine-arginine-arginine (Ac-EEMQRR; Argireline), and the tripeptide copper glycine-histidine-lysine (Cu-GHK).

### *Mechanisms*

The peptide pal-KTTKS is a fragment of human dermal collagen that stimulates new collagen production and has been proposed for wound healing. The synthetic pal-KTTKS is also functional in stimulating collagen production in vitro. In addition, at extremely low levels (parts per billion) in culture, pal-KTTKS reduces excess dermal GAGs which contribute to an antiwrinkle appearance effect. Like KTTKS, GHK is also a fragment of dermal collagen. Copper is a required factor for activity of lysyl oxidase, an enzyme involved in collagen synthesis. Ac-EEMQRR is described as a mimic of botulinum neurotoxin (Botox), which functions by inhibiting neurotransmitter release, thus “relaxing” the muscles involved in defining facial wrinkles.

An important challenge is delivery into skin because peptides are poorly penetrating, especially as the number of amino acid residues increases. An approach to that problem is the addition of a lipophilic chain (e.g., palmitate), which can increase skin penetration several fold over the underivatized peptide. An additional challenge is the cost. As the number of amino acid residues increases, the cost of the peptide can increase dramatically. The consequences are that only low levels of a peptide can be used in the product, which is acceptable if the peptide is potent or the finished product cost to the consumer must be high.

### **Sugar amines**

#### *Forms*

Many materials fall within the broad category of sugar amines, with some widely known ones being the hexose amines glucosamine and N-acetyl glucosamine (NAG).

#### *Mechanisms*

Glucosamine and NAG are precursors to the biopolymer hyaluronic acid, which is an important water-binding structural component of skin in the epidermis and the dermis. Topical use of the hexose compounds thus can improve skin moisturization and also fine lines/wrinkle appearance by building skin structural matrix. NAG has been discussed as an exfoliant, interfering with the cross-linking between corneocytes. Glucosamine has inhibited protein glycosylation in vitro, inhibiting activation of protyrosinase to the active enzyme tyrosinase and thus inhibiting the production of melanin. These materials also have anti-inflammatory properties.

For glucosamine, the challenge is stability. It readily undergoes a Maillard reaction leading to a brown polymeric product. This can be managed to some extent by use of antioxidants and acidic pH. NAG is substantially more stable and thus lacks this challenge. Both materials at high doses (e.g., above 2%) can be sticky in formulation, which can impart aesthetic negatives.

### **Ceramides**

#### ***Forms***

There are many ceramides and ceramide analogs. This contribution will not focus on any particular material but rather discuss them as a group.

#### ***Mechanisms***

Ceramides are lipids essential for a normal stratum corneum water barrier. The other key lipid components of the barrier are cholesterol and fatty acids. All three are required and occur in an approximately equimolar mixture in the intercellular space in stratum corneum, but ceramides have received more attention. Externally supplied ceramides function by incorporating into the intercellular lipid of stratum corneum to replace the depletion that occurs with aging and environmental damage such as from surfactant exposure. The most effective therapy is described as a mixture of ceramides with the other two barrier lipid components.

Ceramides are oil-soluble. As long as the dose of ceramide is not high, it should incorporate into the oil phase of a formulation without difficulty. Ceramides can be expensive though, such that use of high concentrations is a cost challenge.

### **1.3.4 Metals**

#### ***Forms***

Of the many metals, cosmetic products typically contain only a few, among them zinc, copper, selenium, strontium, magnesium, and manganese, as salts and complexes with organic compounds. A few examples are zinc oxide, copper peptide, and selenomethionine.

#### ***Mechanisms***

Metals have specific functions in the skin, often associated with their role as required cofactors in the activity of metalloenzymes, and therefore, the mechanisms associated with individual metals are widely varied. Certain metalorganic compound complexes such as pyrithione-zinc and selenium sulfide are antifungal agents that are effective as antidandruff agents.

Zinc is also associated with the antioxidant proteins superoxide dismutase and metallothionein, so zinc oxide has antioxidant potential as a source of zinc for synthesis of these proteins. Copper is a cofactor for many proteins, including lysyl oxidase and prolyl hydroxylase, enzymes that are important in collagen synthesis. Selenium is a cofactor for the antioxidant enzymes glutathione peroxidase and thioredoxin reductase.

Some metals and their complexes are colored (e.g., copper is blue-green), so that can be an aesthetic challenge at higher doses. Metal salts also can negatively affect product thickeners, requiring substantial adjustment of the formulation. The presence of zinc, for example, can complex with materials such as avobenzone, a common UVA sunscreen, resulting in the avobenzone crystallizing out of solution, causing a yellowing of the product, and significantly decreasing the sunscreen's efficacy.

### 1.3.5 Anti-inflammatories/Botanicals

Numerous cosmeceuticals have been researched to treat sensitive skin, skin affected by rosacea, and photodamage to reduce the redness associated with inflammation. Licochalcone A, from the licorice plant *Glycyrrhiza inflata*, has anti-inflammatory properties. The mechanism of action is thought to be dual inhibition of cyclo-oxygenase and lipoxygenase, thereby reducing proinflammatory cytokines and UVB-induced prostaglandin E2 release by keratinocytes. In this book we are going to discuss about botanicals in individual chapter according to the topic.

### 1.3.6 Polysaccharides

Polysaccharides include the family of hydroxy acids: alpha hydroxy acids (AHA), beta hydroxyl acids (BHA), and polyhydroxy acids (PHA). The AHAs include glycolic acid (grapes), lactic acid (milk), malic acid (apples), and citric acid (citrus fruits) among others. They are considered to be keratolytics because they diminish corneocyte adhesion in the lower levels of the stratum corneum, allowing exfoliation and improvement in skin dullness. They also function as humectants, possibly by increasing dermal glycosaminoglycans, as well as improve stratum corneum barrier function. The exact mechanism of action of AHAs is not known. BHAs, such as beta-lipohydroxyacid and tropic acid, are exfoliants appropriate for acne prone and oily skin. Salicylic acid was once thought to be a BHA, but it is structurally a phenolic aromatic acid. Its lipophilic structure allows it to penetrate into the sebaceous follicles, thus making it useful for patients with oily skin. Salicylic acid is available in a wide range of



concentrations. PHAs can hydrate, moisturize, as well as exfoliate the skin. They include gluconolactone, which may protect against UV radiation in vitro and lactobionic acid, which is both an antioxidant and a humectant. Because of their large size, PHAs do not penetrate the skin as easily and are therefore less irritating to sensitive skin.

### **1.3.7 Pigment Lightening**

The popularity of pigment-lightening cosmeceuticals is because of their effect on out skin tone. The most commonly used pigmentlightening agent is hydroquinone, which works by inhibiting tyrosinase activity. Tyrosinase is the rate-limiting, essential enzyme in the biosynthesis of melanin. It is available both in over-the-counter and in prescription strengths, and it is often combined with other agents such as retinol, AHAs, vitamin C, and topical steroids. Side effects include an irritant contact dermatitis and, more rarely, exogenous ochronosis. Kojic acid is a fungal derivative commonly used in Japan that has been shown to decrease melanin content via tyrosinase inhibition in vitro. It also decreases melanin content in melanocytes and is an antioxidant. One disadvantage is that it can be irritating and is known to cause true hypersensitivity. Like hydroquinone, it is often combined with other cosmeceutical agents or with topical steroids to reduce irritation. Glabridin is the main active ingredient in licorice extract and can inhibit tyrosinase activity. In addition, glabridin has anti-inflammatory properties attributed to cyclooxygenase inhibition. Ellagic acid is a polyphenol widely found in plants such as pomegranates, which inhibits tyrosinase by chelating copper at the active center of this enzyme. It may selectively inhibit melanin synthesis only in UV-activated melanocytes. Fatty acids such as linoleic acid act by tyrosinase degradation without toxic effects on melanocytes.

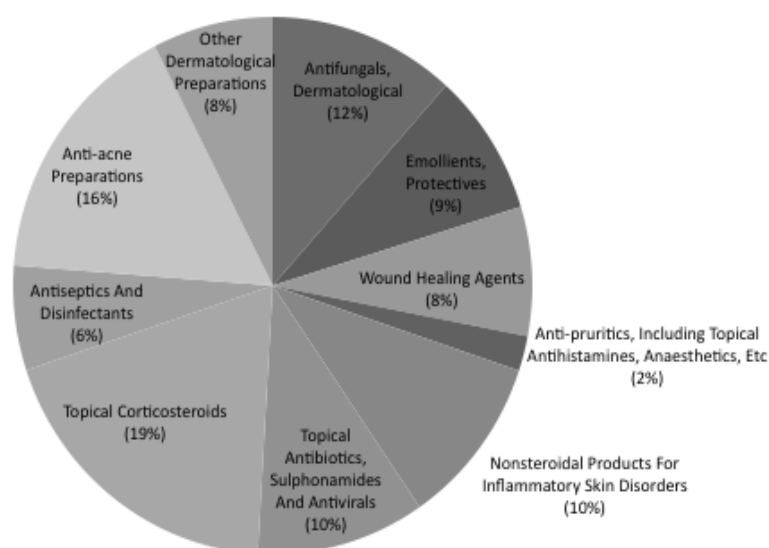
## **1.4 Marketed size**

According to the study conducted by Indian Cosmetic Sector Analysis the cosmetic market is around INR 356 billions. Most of the international companies have introduced their products in India in 1990s. The total Indian beauty and cosmetic market size currently stands at INR 422.3 Billion in 2010 and showing growth between 15–20% per annum, in the US it is about \$6.5 billions. Skin care products occupy half of the cosmeceuticals industry through out the world. Among the skin care products anti-aging market plays major role driven by an aging population seeking to maintain the appearance of youth. Antioxidants will remain the largest chemical category while botanicals and enzymes

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stay among the best opportunities. Injectables and skin care products will register the fastest growth.

According to Confederation of Indian Industries (CII) report, US\$0.68 per capita is spent for cosmetics, which might be lower than some other countries, but this indicates a growing awareness among consumers. There are two major factors that are saying the buying decision among women here. First obviously is the television and media exposure they have today. The other not so obvious one is the corporate dressing culture, which slowly is evolving in the Indian market.



**Fig. 1.1** Global Therapeutic Dermatology Marketsplit by Product Class.

[Colour Fig. on page 393]

### 1.5 Conclusion

The cosmetics industry today holds a unique position. It is characterized by highly competitive marketing strategies and depends on the ability to introduce rapidly new innovative products into the market place. On the other hand, dermatological research may also proceed in the cosmetic field while in-depth research may be conducted with regard to therapeutic applications. Cosmetic companies are permitted to create and market products that are known to have an effect on the structure and function of skin, with little regulation. Most consumers believe that cosmeceuticals

are regulated and tested as drugs. Consumers trust that ingredients have been tested for safety and that claims made in advertisements are real.

One can easily conclude that cosmeceuticals will continue to evolve in parallel with advances in our understanding of skin biology, along with improved methods of measuring the benefits that may be provided by well-engineered skin care products. But we have to consider the changes in the science and technology, so clinicians, scientists and dermatologists have to update their knowledge in this field to produce high quality products with safety.

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